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# Edinburgh Medical Journal

January 1949

## JUDGMENT IN CARDIOLOGY

By RICHARD W. D. TURNER

### PART I

THIS paper deals with a number of practical problems in cardiology which are of common occurrence and a source of difficulty to students, post-graduates and sometimes to physicians. Whether the fault lies with those who learn or those who teach, there may be some profit in collecting a few of these problems together for reconsideration.

It has been said that the very essence of cardiovascular practice is the recognition of early heart failure and the discrimination between different grades of failure. Perhaps it would be better to stress the importance of the early diagnosis of heart disease, accurate assessment of the individual case and, where possible, prophylaxis. Thereby, failure may be prevented or at least postponed, unnecessary invalidism avoided and such conditions dealt with as are amenable to curative treatment. Moreover, there is room for improvement in the management of patients. Accurate assessment must necessarily precede sound judgment and to this end certain aspects of cardiology may be considered worthy of special emphasis. The detection of enlargement of the heart or of its individual chambers is so important that radio-scropy should be part of the routine examination. Precise diagnosis in congenital heart disease is an essential preliminary to surgical treatment but apart from this aspect, in these cases as in so many other cardiac conditions, it is just as important to see that the patient does not do too little as to ensure that he does not do too much. Rest and restrictions are often abused. Penicillin may clear the infection in subacute bacterial endocarditis, but this complication should be prevented or at least diagnosed very early. Hypertension is not a sufficient diagnosis. Each case should be reviewed from the point of view of possible surgical treatment. Great care is needed in the assessment of pain which is suspected, whether by the doctor or the patient, of being cardiac in origin. The psychological factor which is present in nearly every case of real or suspected heart disease must be kept ever in mind and actively treated.

Finally, some of the problems of added sounds and murmurs will be discussed in detail. These are all matters which call for careful consideration if our patients are to receive the best advice and counsel.

A Honyman Gillespie Lecture delivered in the Royal Infirmary on 12th May 1947.

*Enlargement of the Heart.*—It may be possible to tell if the heart is enlarged by clinical methods and, in this respect, palpation is of more value than percussion. Palpation of the apex beat will always give some information of value, often mainly qualitative, but there are fallacies in referring its position to the mid-clavicular line. How rarely does a student or a doctor identify precisely this mid-clavicular line, compared with the frequency with which these observations are recorded. Indeed, some may never have performed this rather difficult task. In men, the nipple line is surely reliable, in that its position is reasonably constant. In women, measurement from the mid-sternal line is preferable, but allowance should be made for the width of the chest. This serves well enough as a rough and ready guide, provided there be recognition of its limitations.

Palpation may reveal enlargement of the heart to the left or the right, though this does not necessarily correspond with enlargement of the left or right sides of the heart. Enlargement of the right ventricle, for example, is usually to the left in the first instance. Frequently, enlargement of the pulmonary artery or conus can be felt and gives useful information. Occasionally palpation may reveal some other abnormal pulsation, for example a huge left auricle pulsating in the right axilla, but it cannot reveal slight degrees of cardiac enlargement, nor structures out of contact with the chest wall. It is not always possible by clinical methods to be certain that apparent enlargement is not merely due to mediastinal displacement.

The presence of fibrosis, hydrothorax or pleural effusion will probably not be missed by careful examination, but a common source of error in apparently healthy individuals, is displacement of the mediastinum from slight degrees of scoliosis. In routine examinations, for example in recruits or for life insurance, the apex beat may be found outside the nipple line and the patient referred for an opinion on the cause of this apparent enlargement of the heart. In the absence of other evidence of disease, the diagnosis may be suspected in finding the left shoulder higher than the right (and the left nipple higher than the right), and this may be readily confirmed on the X-ray screen *when slight rotation will correct the apparent displacement* (Fig. 1a and 1b).

The limitations of percussion will be generally admitted. Difficulties are reflected in the varying area of cardiac dullness favoured by different authorities. Emphysema, obesity and mammary development, present obvious hazards. It is no more reasonable to lament the decline in the reliance placed on percussion than to lament that physicians no longer rely on feeling the pulse to estimate the blood pressure. I cannot do better than refer to John Parkinson's Lumleian lecture on enlargement of the heart in 1936.<sup>5</sup>

He referred to percussion as a subjective method with a diversity of individual convictions and varied methods of performance. The personal factor is enormous and it is difficult to avoid percussing

pre-conceived ideas into the cardiac outline. "Surely," he said, "the time has come to revise our opinion of this primitive expedient which had to serve in the past but has now outgrown its usefulness. . . . The method is sterile in that nothing has been added to medical progress through cardiac percussion since the beginning of this century. . . . No organ is so well placed for X-ray inspection as the heart, surrounded as it is by translucent lung and, by rotation of the patient, it can be viewed from every angle. We can see the volume of the heart and its vascular extensions and meanwhile watch the contraction of its constituent parts. . . . More faithful witnesses are eyes than ears. . . . Radioscopy goes far beyond the dreams of past masters or artists of percussion. It would not do to say it is not readily available. It is available for a trivial surgical or dental effect, so why not to reveal a heart in its fullness? . . . No longer should we tell of the Professor who, by knocking at the front door could find out who is in the drawing-room."

X-ray films in the anterior and oblique positions are of limited value. Slight degrees of rotation and the height of the diaphragm may be misleading (Fig. 2a and 2b). By screening, not only can the absence or presence of enlargement be ascertained with considerable accuracy, but enlargement of individual chambers, even in slight degree, can be appreciated. Very often the outline of the heart is characteristic of certain lesions, even in an early stage. Moreover, the thoracic aorta can be studied throughout its length and dynamic pulsations observed. Likewise, the pulmonary artery and its main branches, the lung fields, and the movements of the diaphragm can be examined. Minor degrees of hydrothorax are frequently revealed during a screening examination and occasionally information of a different kind, for example, the demonstration of a hiatus hernia of the diaphragm, reveals the cause of pain mimicking that of ischæmic heart disease. The presence or absence of enlargement is a fundamental matter in every case. Always important when present, its absence may be strong confirmatory evidence of functional disease. There are occasional exceptions as in cases of coronary disease, constrictive pericarditis and sometimes in congenital heart disease when there may be no enlargement but, in such instances, other evidence is available from the history or physical examination or the electrocardiogram. Too strong a plea cannot be made for the screening of every heart in which disease is manifest or suspected. The time will surely come when screening will be part of the routine assessment of every case, not an accessory method, but just as much part of the examination as inspection, palpation and auscultation. The very suspicion of heart disease raises questions which will affect the whole life of the individual concerned.

Even when the diagnosis is clear, screening gives added information in assessing the severity of the condition. On occasion, a diagnosis will be made or suggested which cannot be made, or has been missed

by clinical examination. This is by no means infrequent in mitral stenosis, even by experienced observers. Again, in syphilitic aortitis, where incompetence of the valve is not present, radiological change is the earliest detectable abnormality. In auricular septal defect, a characteristic dynamic picture is seen. Usually the diagnosis is not possible by clinical methods and may easily be mistaken on an X-ray film. No one would pretend he could detect early changes or the enlargement of individual chambers with any certainty by percussion. Another point worthy of emphasis is that congestion of the lungs can be detected long before crepitations can be heard in the lungs.

The limitations and misleadings of percussion are widely recognised ; this plea is for the routine employment of radioscopy in clinical medicine. One cannot believe that any doctor could fail to be impressed by the degree of added insight given, or the frequency with which his clinical judgment is corrected—and this no matter how careful, skilful or experienced the observer. Not seldom are the clinical impressions of the expert refuted by the X-ray findings, as he would be the first to admit. It is no longer sufficient to say that the heart is enlarged, any more than to say the heart is irregular, without further qualification. It is necessary to say which chambers are enlarged and in what degree, and to describe the state of the great vessels. Nor is this examination best made by the radiologist but by the physician who has just examined the patient. Just as a written summary of the history by another person cannot take the place of one's own impression of a patient, so a written report cannot replace the visual impression of the heart to the physician. The physician and the patient will benefit from the correlation of the complementary clinical and radiological findings. Only in this way can progress be made. It is manifestly impossible for a radiologist to spend much time in the wards, whereas it is perfectly simple for the physician to learn the art of screening the heart and lungs with little knowledge of the underlying physical principles and technical details of the apparatus. Moreover, now and then, as opportunity offers, the physician will have his findings corroborated or confounded by the pathologist and thereby his judgment will be improved. Again, and perhaps not least, there may be occasions when a judicious running commentary at the time of screening may, consciously or subconsciously, do much to fortify the patient in one's reassurance as to the absence of organic disease. This cannot be deemed unscientific, for frequently it is the screening examination which fortifies the doctor.

There may be a tendency in these days for the student to hope that an accessory method of investigation, preferably undertaken by someone else, may save him the trouble of thinking and supply the answer to his diagnostic problems. This is not to belittle the essential powers of clinical observation but to emphasize that screening of the heart is but an extension of the eyes to the moving, living field beyond their unaided reach. Nor is this a reproof for the modern generation that

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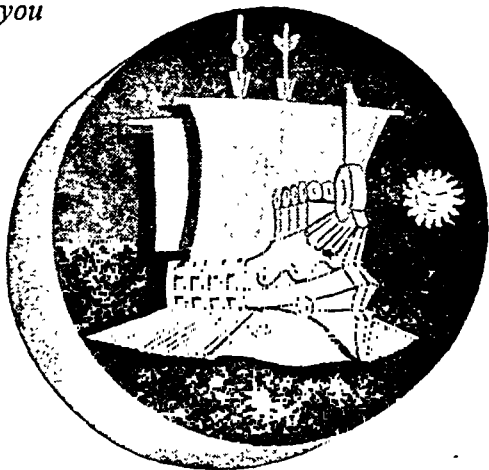
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they are less skilled in using bedside methods. Experience has clearly shown that some such methods are found wanting. However, confidence will only be shaken by putting the matter to the test.

No decision which materially affects a person's way of life should be made without adequate assessment and, whereas for example, in the presence of failure, a study of the size and outline of the heart may be considered a refinement, in many instances, it is an essential part of the assessment. For want of this, many mistakes are made, even by experienced physicians.

*Congenital Heart Disease.*—The diagnosis of congenital heart disease in childhood and adults is now more exact, and accuracy is becoming more important since certain lesions can be dealt with surgically. In infancy, multiple defects are likely to be fatal, but it is unwise to be dogmatic about prognosis in the early years. Unwarranted despair is often engendered in the parents on the strength of blue attacks or a murmur when subsequent progress refutes the early pessimism. Still to-day, children of school age are denied normal activity and education on account of a murmur, even though otherwise well and of normal development. Special schools with arrangements for transport, rest and a midday meal have their place, but surely a child should be allowed to attend a normal school and lead a full, active life, unless manifestly handicapped, thereby avoiding unnecessary restrictions and the harmful effect of believing itself to be abnormal. Here too, radiology is of immense value in aiding the assessment. Even in childhood, neurosis can be carefully combated and prevented. There is need for balance in the surgical treatment of patent ductus arteriosus. It may well be that in childhood, when the conditions for operation are most favourable, all established cases should be ligated. However, after adolescence, if growth is proceeding normally, and there are few or no symptoms, it may be wisest to let things be and for that individual to remain under the care of the practitioner or be referred for periodical review by a physician. At this age, the operative mortality is by no means negligible.

*Pregnancy.*—Much has been written on heart disease in pregnancy. There is close agreement about the risks involved, and about those in whom pregnancy should be avoided or terminated. With due precautions and adequate rest, most patients can be shepherded safely through. The question of terminating pregnancy is rather different from that of giving advice on avoiding a family. Other issues are involved and the doctor must take his decision on safety for the mother. Early termination is simple and safe but, after the fourth month, the risks involved are about equal to those of going to term.

If the patient is first seen in failure, rest in bed is essential and probably will be for the remainder of the time. It is worth remembering that cardiac failure very rarely occurs first during labour or the puerperium. The real strain often comes later, with all the work an extra



child brings. This is especially the case if auricular fibrillation begins about the same time. Most patients with mitral stenosis begin to fibrillate about the time they are 35 to 40. A toddler and auricular fibrillation may literally be a heart-breaking combination whereas, if the child is old enough to help in the home, by the time fibrillation supervenes, it is a very different matter. Perhaps this is the aspect of heart disease in pregnancy which needs most emphasis to-day. The problem is largely one of age. Other things being equal, the girl in her early twenties has little to fear from two or three pregnancies. However, in these times, many a family begins in the thirties. Thus, if girls with heart disease must marry and bear children, they should be encouraged not to delay. In deciding on the size of the family, economic status and the possibility of help in the home, are major considerations.

*Hypertension.*—Symptoms are too readily attributed to moderate high blood pressure. In the stage of hypertension before any effect on the heart can be detected, there are usually no symptoms apart from those due to neurosis, which may be largely doctor engendered. Sometimes there is a complaint of headache, which may really amount to a sensation of pressure or fullness in the head, and which is related to posture. Very occasionally there may be palpitation, but heart disease is probably the least common cause of this symptom. A diagnosis of hypertension is not sufficient. Every patient is worth thorough clinical assessment before a diagnosis of benign essential hypertension is reached or a decision on treatment is made. Nephritis and endocrine disorders will not readily be missed, but unilateral renal disease should be excluded as a routine. Renal ischæmia associated, for example, with the shrunken kidney of old pyelonephritis may be responsible for the hypertension and, if not of too long duration, nephrectomy may relieve the condition. This really means that an intravenous pyelogram should be carried out in every case, for the urine will not necessarily be abnormal at the time of examination. It is a good habit always to feel for the femoral pulses, especially in the younger patients, in order to exclude coarctation of the aorta, for to-day there is the hope of successful surgical treatment. A common error is failure to examine the fundi. Malignant hypertension tends to occur in an earlier age group and the prognosis is so bad that an error of judgment is serious. Recently two men were seen who had consulted their doctor on account of visual disturbances and were referred, not to an oculist, but to an optician for spectacles. In each, a few months later, malignant hypertension with papilloedema was found and this must have been present at the time of the onset of symptoms.

In benign essential hypertension, the prevention of neurosis is important from the very beginning. The patient should never be told the actual figures of his blood pressure or when necessary, it is justifiable to mislead by quoting the diastolic reading. It is a good

habit to refer to the condition as "only blood pressure." It may not be possible to assess the situation at one examination but only by periodical review. Often the pressure falls on rest or sedation. The various factors can be assessed without engendering neurosis if this is positively guarded against from the beginning. Explanation and re-assurance are essential and time given to these can never be wasted. Not only must genuine symptoms attributable to the hypertension be critically assessed from the point of view of progression, but the objective changes must be carefully watched. This will mean periodical assessment of the diastolic blood pressure and especially the basal blood pressure after sedation, the size of the heart, the fundi, the urine and renal function, the electrocardiogram and evidence of left ventricular failure. The latter may include triple rhythm, pulsus alternans, weakening of the mitral first sound with accentuation of the pulmonary second sound, a mitral systolic murmur, a decapitated blood pressure, hilar congestion and œdema on the screen and a negative T wave in lead I of the electrocardiogram.

There is not yet agreement about the advisability of sympathectomy in essential hypertension. The collective statistics from America on large series are impressive, but it is difficult to believe that all cases are selected critically, and that too many are not undergoing unjustifiable prophylactic operation against possible evil effects of hypertension in the years to come. Hypertension can be benign for so long, especially if it occurs in late middle life and especially in women. Symptoms are often not really attributable to the blood pressure itself. However, under fifty years of age, and especially if the condition can be shown to be progressive, the problem must be faced, for there is no adequate control of symptoms by medical means. Perhaps sympathectomy should be considered in three groups of patients but from different points of view, so that the operation, even though it may be an empirical one, may not be brought into disrepute. In the first group come those who have benign essential hypertension of at least moderate degree, symptoms attributable to raised blood pressure and evidence of progression, but little renal failure. Here the operative risk is small and the chances of improvement, though difficult to assess in advance, considerable. In the second group come those with malignant hypertension who have papilloœdema and even mild left ventricular failure but yet retain reasonably good renal function. Their prognosis is otherwise utterly hopeless, and remarkable improvement may sometimes follow sympathectomy with regression of the eye changes and cardiac failure. Here, of course, the operative risk is considerable.

Finally, there is the difficult early age group with a slightly raised blood pressure discovered on routine examination and entirely free from symptoms, but generally considered to be candidates for more severe hypertension later on. Before this problem can be decided, most careful assessment of large, well controlled series will be needed. There will be a natural reluctance, felt by many, to submit such healthy

young people to a major prophylactic operation, particularly whilst the evidence is so slender. For the time being the best plan probably consists in keeping the patients under careful observation. Review at six-monthly intervals will detect any deterioration and help in deciding about the advisability of operation.

*Pain.*—More often than not, the differentiation between the pain of ischæmic heart disease and that of psycho-somatic origin, can be confidently made on the history, but there are exceptions. Ischæmic pain may be atypical in situation or quality, or the patient may be a poor observer or lack adequate powers of description. Actually, where there is doubt, the pain is most often of functional origin. Help may be given by the electro-cardiogram which shows significant changes in about 50 per cent. of patients with angina pectoris and in a considerably higher percentage if taken following an exercise test. It is remarkable how clear cut is the history of ischæmic pain in most instances: an unemotional account of a single arresting symptom and, by contrast, the multiplicity of complaints of the neurotic patient. Sometimes it is difficult to delve beneath the super-imposed functional state and the difficulty increases with the number of observers who have taken the history. The problem may be solved by getting back to the first attack. Sometimes, one is forced to await developments and keep the individual under observation, meanwhile making few restrictions and trying the effect of glyceryl trinitrate. In either case, rest in bed and relaxation for a tired man may relieve the pain, even if this does not assist in differential diagnosis. It is sometimes assumed that any chest pain which is referred down the left arm must be due to angina pectoris, but this is far from being the case. It may accompany any pain felt in the upper left quadrant, but pain referred down the right arm or both arms, is almost invariably based on organic disease. Functional pain of left mammary type without relation to cardiac ischæmia, may be super-imposed on organic heart disease and is especially common in mitral stenosis. It should be carefully differentiated and actively combated in all cases, whether super-imposed or primary. The pain and disability are real enough and very natural anxiety may be marked. Treatment with adequate explanation and firm reassurance is usually successful but symptomatic measures and perhaps the local injection of procaine may be necessary. It is a common error for doctors to put such individuals to bed for long periods. Not long ago, a girl with mitral stenosis and characteristic left mammary pain was put to bed by her doctor on this account for no less a period than one year. When she was finally allowed up, she found to her dismay that the symptoms were still present and decided to seek further advice. She had a mild degree of mitral stenosis, normal rhythm, little enlargement of the heart and there was no possibility that there had ever been cardiac failure. It was not easy to combat her fears and persuade her to return to full activity as soon as possible, nor easy to avoid discrediting the doctor.

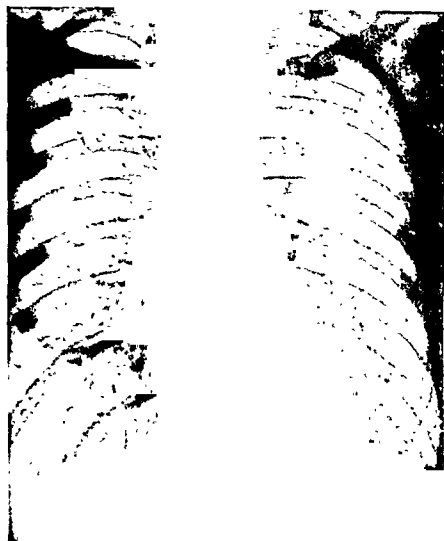


FIG. 1*a*.—Displacement of apex of heart by scoliosis. Note relatively high left clavicle.



FIG. 1*b*.—Same case showing "correction" of displacement by slight rotation of the patient.



FIG. 2*a*.—Effect of inspiration (2*a*) and expiration (2*b*) on the height of the diaphragm and position of the heart.



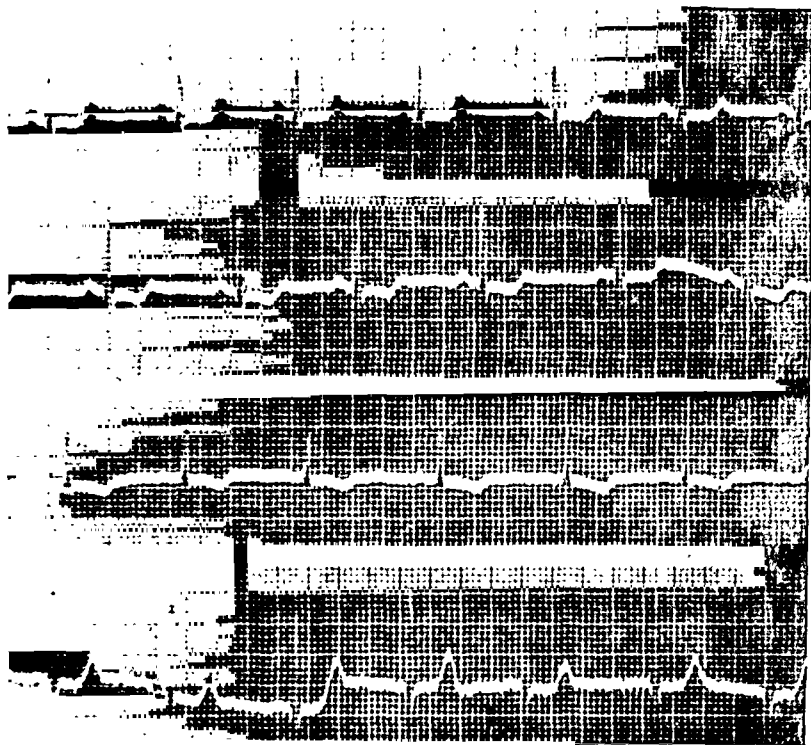


FIG. 3.—Case X. E.C.G. Leads I, II III and lead 4R.



FIG. 4.—Case X. Gummatous plaque occluding one coronary ostium.



There is a danger in loose terminology. Fortunately, such terms as pseudo-angina are dying out, but a few months ago a physician was heard to state that he had suffered from typical angina of fibrositic type! It is no wonder that students are not always clear in their descriptions. It is better to avoid the term *præcordial*, because only in the mind of the author is it clear whether the pain is retro-sternal, under the left breast or somewhere in between. If in the region of the breast, it is not in fact, *præcordial*. Moreover, in functional cases, there should be no reference to the heart. It is also best not to use the term *angina pectoris* in front of the patient, for to the lay mind it tends to be associated with impending sudden death.

As in hypertension, so with ischæmic pain, it is worth while to exclude the presence of any relevant underlying disease in every case, notably syphilis, aortic incompetence and anæmia. Rheumatic aortic incompetence may occasionally give rise to typical ischæmic pain, even in young people. Syphilis, especially in all those under 50 years of age, is best excluded as a routine by radioscopy and a Wassermann reaction. The frequency with which nocturnal angina decubitus is due to this cause, is noteworthy.

During the recent war, with the modern treatment of venereal disease, it is probable that in dealing so promptly with the gonococcus, the spirochæte may not have been entirely eradicated but rather temporarily submerged, so that we may expect to see an increase in the incidence of specific aortitis in the years to come. This is especially true in that it was clear, in certain countries, that the spirochæte was of a particularly virulent type. (Extra-genital primary chancres were a commonplace, as were secondary and tertiary lesions with little or no evidence of a primary stage.)

A girl aged 27 gave a short history of pain indistinguishable from that of ischæmic heart disease, but had no abnormal signs that could be detected. X-ray of the heart and aorta was normal, but the electrocardiogram showed evidence of some myocardial change (Fig. 3). In view of the improbability of coronary atheroma in her case, a Wassermann reaction was taken and found strongly positive. A few days later, before any treatment was instituted, she collapsed and died. Post-mortem examination revealed complete occlusion of one coronary orifice by a small plaque of granulomatous tissue (Fig. 4). It is reasonable to believe that many such cases of less virulent degree may be developing in service personnel of all ages and, of course, particularly in men. Specific aortitis may be first detected by the finding of an aortic diastolic murmur in a patient complaining of symptoms related to his heart (for example, ischæmic pain from coronary ostial stenosis, or breathlessness from left ventricular failure). It is well to remember the possibility of this cause for pain in every case of angina pectoris, however unlikely it may seem in the individual concerned. Actually, the earliest physical manifestation is usually dilatation of the ascending aorta on the X-ray screen.



The prognosis of ischæmic pain, secondary to coronary atheroma, is not so gloomy as is sometimes thought. A recent American survey with a ten years' follow-up of more than 3,000 patients, showed that the average five year survival rate was 71 per cent. for women and 58 per cent. for men and that the average ten year survival rate was 49 per cent. for women and 33 per cent. for men. In other words, five years from the time of diagnosis, some 60 per cent. of the patients will be alive, and at the end of ten years half the women and one-third of the men will remain.<sup>6</sup>

*Subacute Bacterial Endocarditis.*—This insidious infection, which seems only to affect the structurally abnormal or damaged hearts, should be suspected in any mysterious fever that lasts more than a few days. Better still, it should be prevented in so far as this is possible. Most often, there is a definite precipitating illness, such as a sore throat or other infection, or some minor operation that results in temporary bacteræmia, such as tonsillectomy or dental extraction. Infections should be taken more seriously than in otherwise healthy people and treated with sulphonamides or penicillin and even minor operations should 'invariably be "covered" by such means for two to three days before and afterwards. It is now well known that penicillin in suitable dosage for an adequate period can and does cure subacute bacterial endocarditis in most cases. Certainly, the patient may still succumb to heart failure from previous valvular or myocardial injury but, whereas a few years ago the infection was nearly always fatal, it need but rarely be to-day. It is hardly necessary to stress the importance of early diagnosis to prevent further damage.

*Abuse of Rest.*—When first a diagnosis of ischæmic heart disease or considerable hypertension is made, a short period in bed may be invaluable to rest a tired man and persuade him that relaxation is possible and that he is not, in fact, indispensable. On the other hand, there are some who cannot abide any form of restriction and insist on dying inconveniently and without preparation. It is curious that, whereas the general rule and practice is to insist on six weeks in bed following myocardial infarction, a patient who has a first attack of paroxysmal nocturnal dyspnœa may be allowed up after a few days or even permitted to carry on, yet the latter affliction is considerably more serious.

The six weeks' rule may be a good one to explain at the beginning of the illness, together with a warning, that at least a further six weeks off work will be required for convalescence. However, in actual practice, provided there has been no subsequent failure or other untoward event, it is frequently both safe and wise to allow the patient up into a chair after three weeks. The danger period will really be over as regards the risk of rupture of the heart, arrhythmia or embolism and none can foretell further infarction nor forestall it by further rest. Indeed, excessive rest is more commonly associated with a second infarction or with peripheral venous thrombosis and

perhaps pulmonary embolism; with pulmonary œdema, general weakness or the development of neurosis. In some cases, restlessness of mind and body is more likely to occur with insistence on bed rest and then three months in one room may be better advice than six weeks in bed. The armchair has many advantages, not the least of which will be the replacement of the bedpan by the commode. Patients with left ventricular failure in particular, are often insistent that they feel better out of bed and may choose the chair for sleeping at night. Moreover, œdema is better in the legs than in the lungs. We should consider what our own attitude would be, and remember the surreptitious activities of our doctor patients.

Relevant to this theme are the restrictions placed on old people and those with incurable heart disease, in the hope of prolonging life. There is really no evidence that mild exertion and exercise is less dangerous than enforced rest. Certainly, many lives are made miserable by unnecessary restrictions. It is natural that fond relations should wish to add to the days that may yet be granted, but the individual most concerned would often choose to die, if not in the saddle, rather in the garden than the bedroom and with a pipe in his mouth and deciding his own diet. Unnecessary restrictions may result only in increased irritability of the patient with adverse effects also on those who watch and wait.

*The Almoner.*—The almoner should be available to advise and help in the management of every patient seeking treatment for heart disease. In normal times, much can be done to advise suitable work when guided by the physician on the degree of exertion permissible. In these days, the Disabled Persons' Act ensures that every firm must employ a small percentage of partially disabled men or women and, in most instances, even sedentary work such as clerks, watchmen and doorkeepers etc., can be arranged for a fair number of persons. Arrangements can often be made for children to be looked after daily in a crèche. In other instances, home helps can be provided to assist the mother in her housework and see to the shopping. Such social services are likely to increase in the future. If the individual cannot go to work, it may be possible for work to be carried out in the home and payment received. Priority certificates can be given for ground floor accommodation. Furthermore, the almoner can see that the patient remains under medical care and that a visit be arranged, should he or she fail to attend as expected. All these factors are important in delaying the onset of cardiac failure, or minimising the stresses and strains which might aggravate it.

*Psychological Aspects.*—Psycho-somatic disturbances are much emphasized to-day and whenever possible, diagnosis should be based on positive evidence in the same way as organic disease. The symptoms of cardiac neurosis are familiar and consist essentially of Gallavardin's "le trépied"; left mammary pain, palpitation and sighing respiration, together with that unhappy band of symptoms

common to neurotic ill-health, exhaustion, faintness, giddiness, trembling, insomnia and so forth.

In this paper, neurosis is used in a very broad sense and no attempt is made to use precise psychological terms. Nor is the term neurotic ill-health meant unkindly. It is not sufficient to make a positive diagnosis of organic heart disease and still less to exclude organic heart disease and let the matter rest. Full explanation in proportion to the intelligence of the individual concerned must accompany re-assurance in either case. A middle-aged patient was admitted with auricular fibrillation. She told how, seven years ago, her doctor had declared her heart was hanging by a single string. It is not suggested that she remembered his words accurately yet surely they must have reflected the impressions created. Indeed, she might be excused from walking delicately, like Agag. Patients regularly pick up such impressions and the fault lies with us in not explaining matters fully.

A man aged 21 was referred for an electrocardiogram by a local Pensions Medical Board. The request was accompanied by nine lines of history which might be quoted in a text-book as an example of neurosis. Nothing was missing and this was followed by a statement that there were no abnormal physical signs and the blood pressure was normal. The diagnosis was stated to be myocardial degeneration. Apart from the financial aspects of the pension, much hard work over a period will be needed to dispel the conviction in this man's mind that he has an abnormal heart.

A soldier was recently referred for an opinion by the surgeons following appendicectomy. He had a persistent tachycardia and presented the typical picture still known as effort syndrome. He said he had often been told there was nothing wrong or been laughed at during the war but could not understand how, if his heart was beating at twice the normal rate, his expectation of life would not be half the normal span. Explanation accompanying the re-assurance had clearly been inadequate.

We must be careful in our choice of words and also remember the dangers of silence. Patients will accept with equanimity the information that they have, for example, kidney or liver trouble. A touch of tuberculosis may be taken lightly but, except perhaps for cancer, there is no fear to equal that of the mildest heart disease; for the heart is known to be essential to life. Robert Marshall, in Belfast, is accustomed in his teaching to refer to this problem of super-imposed neurosis as the bride's cake phenomenon. On contemplating a wedding-cake, one sees, or used to see, a mass of white sugar and icing but no one could tell before the cake was cut, how much was icing and how much cake.

*(To be continued)*



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# THE TREATMENT OF CARCINOMA OF THE RECTUM WITH SPECIAL REFERENCE TO THE PRESERVA- TION OF THE SPHINCTER MECHANISM

By ROBERT MAILER, M.D., M.S., F.R.C.S.(Ed.), F.R.F.P.S.G.  
Surgeon, Victoria Infirmary, Glasgow

"IN the pursuit of ideals it behoves the surgeon to explore the art of surgery to discover methods which will preserve the wonderful sphincteric mechanism with which a beneficent Creator has endowed his peoples, surely one of God's greatest gifts to man."

In these well-chosen words Grey Turner,<sup>28</sup> in his Murphy oration of 1931, expressed the aspirations of many surgeons past and present, who, in the treatment of carcinoma of the rectum, have sought by one means or another to combine adequate removal of the growth with the avoidance of a permanent colostomy.

In this country during the past thirty years surgical treatment of carcinoma of the rectum has been dominated by the teachings of the late Ernest Miles.<sup>23</sup> Up to his time surgeons had been content with a very local excision of diseased tissue extending as a rule no more than an inch beyond the margin of the growth. Based on the studies of lymphatic drainage carried out earlier by Poirier, Cuneo, and Delamere,<sup>26</sup> and on his own observations of the sites of recurrent growth after operation, Miles advocated and practised the widest excision of all tissue within the possible zones of spread. This entailed the sacrifice of the sphincter and made a permanent abdominal colostomy essential. His results, based on the five year survival rate of patients, were so great an improvement on those obtained before this time, that his abdomino-perineal method of rectal resection became the standard procedure, not only in this country, but in many parts of the world. The only criticism of the Miles operation, apart from the permanent colostomy, was that it appeared too severe for some of the older and frailer sufferers from this distressing complaint.

Within recent years there has been a revival of interest in operations designed to preserve sphincter control. This conception is not in any way new. It goes back over seventy years, and while in this country operations directed towards restoration of continuity suffered an eclipse with the advent of the Miles operation, this was not so on the continent of Europe where attempts at restoration of continuity and sphincter preservation always remained more popular.

THE PATHOLOGICAL BASIS OF SURGICAL TREATMENT. The surgical treatment of carcinoma of the rectum is planned on our knowledge of its manner of spread, and of the paths along which this spread takes place. An adeno-carcinomatous tumour spreads in

A Honyman Gillespie Lecture delivered in the Royal Infirmary, Edinburgh, 4th November 1948.

three ways. (1) By direct extension through continuity of tissue. (2) By veins. (3) by lymphatics.

*Direct Extension.*—Spread by direct extension takes place in two directions: (1) on the mucous surface of the bowel, (2) through the thickness of the bowel wall.

Surface extension progresses very slowly, and more slowly in a longitudinal direction than in a transverse. Longitudinal extension within the submucosa is often a little wider than in the mucous membrane, but it is rare, according to Miles, to find an extension much above and below the margins of the surface growth. Meanwhile the more important deep infiltration through the muscular coat is taking place. Though also a slow process, the growth ultimately invades the peri-rectal fat and reaches the fascia propria of the rectum. It is only then that adhesion to sacrum, uterus, prostate or bladder can take place, though this may take a year after the first appearance of objective symptoms.

*Venous Spread.*—Once the tumour invades the submucosa, it reaches an area richly supplied with small veins. Later when it has

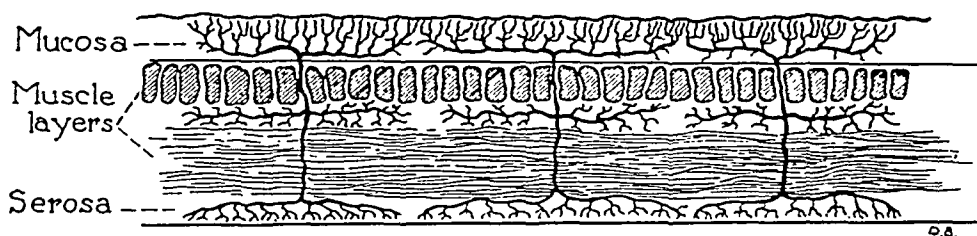


FIG. 1.—Diagrammatic representation of the arrangement of lymphatics in the wall of the rectum (after Leitch).

reached the peri-rectal fat, it comes into close proximity to hæmorrhoidal veins and their tributaries. According to Dukes and Bussey,<sup>9</sup> there is evidence of venous spread in 17 per cent. of all cases, but this venous spread varies according to the histological grading of the tumour, being only 5-10 per cent. in grades i and ii of the Broders classification, but rising to 25-30 per cent. in grades iii and iv tumours. Roughly half the cases in which venous extension is demonstrated show hepatic metastases and alternatively in 25 per cent. of cases in which the veins are apparently free, the liver may show involvement. Liver metastases may be present in cases in which the primary growth is relatively small and mobile. This has some practical importance, as resection of the growth with anastomosis can be carried through as a palliative operative in these cases.

*Lymphatic Spread.*—From the surgical standpoint this mode of spread is the most important. Anatomists describe lymphatic plexuses both in the submucous coats and also between the muscle layers of the rectum.

While these plexuses within the rectal wall have been regarded as communicating with the pelvic colon above and the anal canal below, in actual practice metastases do not seem to be met with in

the wall of the rectum. This would suggest that the lymphatics of the submucous and muscle coats do not exist as a continuous plexus, but are arranged as decussating arborescents from which the collecting stems pass through circular and longitudinal muscle coats to reach lymphatics in the peri-rectal fat or in the subserous layer (Fig. 1). This would explain the restricted longitudinal spread in the wall of the rectum which has been stressed so much by pathologists in recent years.

From the peri-rectal fat the spread is mainly upwards along the lymphatics accompanying the hæmorrhoidal and inferior mesenteric vessels. In addition, there is a lateral zone of spread through the lymphatic network situated between the levator ani and pelvic fascia, and a downward zone of spread to the ischio-rectal fat, the external sphincter muscle and the peri-anal skin (Fig. 2).

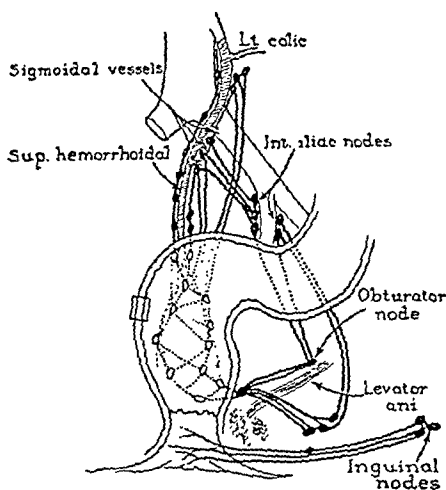


FIG. 2.—Routes of lymphatic spread in carcinoma of the rectum (after Miles).

Once the lymphatic vessels have pierced the wall of the rectum they enter the ano-rectal glands which lie over the surface of the rectum in association with branches of the superior hæmorrhoidal vessels. Miles stressed the upward zone of spread as by far the most important but he felt that lateral and downward spread were also important, and this irrespective of the position of the tumour.

**MODIFICATION IN THE MILES CONCEPTION OF SPREAD.**—The first comprehensive study to assess the importance of downward spread was carried through by Westhues<sup>33</sup> in Germany in 1930. He showed that the extent of malignant cell invasion in the rectal wall did not exceed 1.5 cm. beyond the visible and palpable edge of the growth and he postulated that the sphincter could be saved if there was 4 cm. between the lower end of the growth and the upper end of the sphincter.

With regard to spread in the connective tissue and lymphatics outside the rectum only 1 out of 210 metastatic nodes examined was below the lower edge of the growth, the remainder being at the same level or above. Glands containing cancerous deposits were not found



higher than 10-12 cm. above the growth, ordinarily about the level of the promontory. In the meso-sigmoid, glands were found only rarely, and if present were only in cases which could not be cured by any radical operation.

These findings were largely confirmed by Dukes<sup>10</sup> at St Mark's Hospital, who showed that lymphatic spread in a downward direction tended to occur only if lymphatic routes at a higher level were blocked by malignant cells. Similar conclusions were reached by Wood and Wilkie,<sup>34</sup> Gilchrist and David,<sup>12, 13</sup> Waugh and Glover<sup>14</sup> and others.

TABLE I

*Incidence of Retrograde Nodal Metastasis in Carcinoma of Rectum and Recto-sigmoid. Review of Literature*

	Total Cases.	Positive Nodes-Cases.	Nodes involved below Lesion-Cases.	Distance below Lesion-cm.	Site of Lesion.
McVay, 1922 . . . . .	100	47	1	0-1	Ampulla
Wood and Wilkie, 1933 . . . .	100	51	0	...	...
Westhues, 1934 . . . . .	74	?	1	1	?
Gabriel, Dukes and Bussey, 1935 .	100	62	2	0-1	Upper rectum (8 and 9 cm.)
Gilchrist and David, 1948 . . .	153	...	7	1-5	Ampulla
Coller, Kay and MacIntyre, 1940 .	33	22	1	1-5	Recto-sigmoid
Grinnell, 1942 . . . . .	75	41	1	1	Ampulla (6 cm.) *
Total of cases in the literature .	635	239+	13	...	...
Glover and Waugh, 1944 . . . .			27 6 1 1 1	0-1 1-2 2-3 3-4 6-7	Upper rectum, recto-sigmoid and lower sigmoid
Total of Glover and Waugh's data	100	100	36		

\* Above the pectinate line.

These studies are summarised in Table I which is from Glover and Waugh's valuable contribution. Apart from Glover and Waugh's own series, it will be seen that in a total of 635 operative specimens only 13 showed involvement of lymph nodes below the level of the lesion, and of these in only Gilchrist and David's series was involvement as low as 5 cm. noted. Glover and Waugh's cases on the other hand comprised 100 of the most advanced from an available series of 2206. These showed 36 specimens with involvement of lymph nodes below the level of the lesion. In 33 the involvement did not extend beyond 2 cm., but the 3 remaining specimens showed involvement of nodes from 2-7 cm. below the lesion. It seems reasonable therefore to accept the conclusion that downward lymphatic spread is uncommon. Wayne Babcock<sup>2</sup> put its frequency at 6 per cent. of all cases, and it occurs only in advanced cases in which the upward lymphatic routes are

already blocked. Such cases are probably outwith the possibility of cure by any operation, no matter how radical.

THE DISABILITY OF PERMANENT COLOSTOMY.—All surgeons agree that permanent colostomy should be avoided whenever possible, but many feel like Lahey that it is the price which must be paid for the best chance of long term survival after operations for carcinoma of the rectum. On the other hand, opinions differ as to how much actual disability is caused by a colostomy. Some surgeons report instances where patients were driven to suicide, or in less extreme cases, where colostomy caused much misery and unhappiness through loss of occupation, or broken social relationships. Others, including Lahey,<sup>18</sup> Rankin,<sup>27</sup> and Gabriel,<sup>11</sup> whose experience in this sphere is very extensive, emphasise the relatively slight inconvenience of a well controlled colostomy, and relate that a good proportion of their patients were able to return to their occupations and to take their place in society with little or no apparent difficulty.

The eagerness on the part of patients to avoid colostomy is understandable, though here again their attitude is often coloured by their experience of a friend or relative who has had a palliative colostomy for inoperable disease and where the colostomy appeared only as an added misery to a person going steadily down hill.

The experience of a general surgeon in these matters is perhaps more limited, and while one has seen a number of patients who were able to return to their former work and even on occasion to occupy responsible public positions, these were on the whole the exceptions and they belonged to a strong willed and determined group of men and women who regarded the colostomy problem as just another hurdle in life which had to be successfully surmounted. The remainder, perhaps the majority, apparently cast in less heroic mould, could not rise superior to the feeling of social inferiority, retired from all their former activities and led a cloistered life at home.

The aim of surgery should be to offer something more than mere prolongation of life, for life has breadth as well as length. Whether in the endeavour to restore patients to a fuller, happier and more normal life, the surgeon is justified in recommending any other than the procedure which is recognised as the surest guarantee against recurrence, raises a problem bordering on the realms of philosophy and medical ethics.

Under the best conditions, the abdomino-perineal operation offers a 5 year survival to approximately half the patients submitted to it.

Most recurrences after operation develop in the first three years and it has been shown that once the 5-year period is over the mortality curve for those patients who have survived, runs parallel to the general mortality curve for the same age groups (Fig. 3). This means that in advocating a less extensive procedure than the abdomino-perineal operation of Miles, the surgeon is taking a risk which is only justified if in his selection of suitable cases he can obtain results comparable

in mortality and in non-recurrence rate with those obtained by the standard procedure.

My own interest in resection of the rectum with restoration of continuity arises from yet another consideration. Though we are accustomed to think of carcinoma of the rectum as a disease which may attack even the youngest age groups, a study of the Registrar General's return for Scotland (1945) reveals that the great bulk of deaths from this disease occur between the ages of 60 and 80. There are roughly three times as many deaths from carcinoma of the rectum in the 60-80 age group as in the 40-60 age group, in spite of the fact that there were twice as many people in the latter group as in the former. In dealing with carcinoma of the rectum we are dealing in the main with old people, and post-war studies on the problems of old age

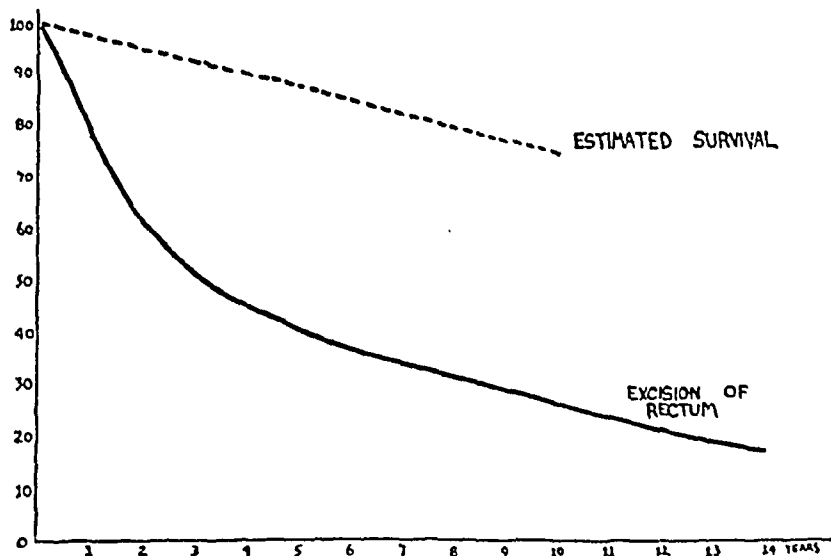
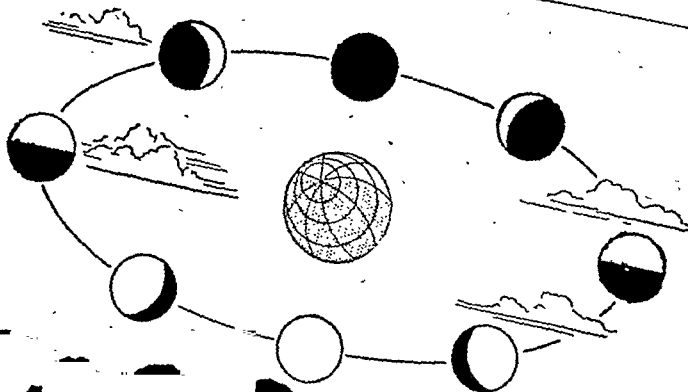


FIG. 3.—Survival rate of rectal cancer treated by excision compared with estimated survival of a control population similar in age and sex (after Dukes).

have thrown into relief that a greater proportion of these people are living alone and with less access to help and attention. As in these old people the disease is more likely to belong to the relatively benign type, the avoidance of the added burden of colostomy seems well worthy of consideration.

**THE EVOLUTION OF THE SURGICAL TREATMENT OF CARCINOMA OF THE RECTUM.**—It is impossible to give more than a brief outline of the steps by which the modern treatment of rectal carcinoma has been evolved. The restricted perineal operation of Lisfranc,<sup>19</sup> first performed in 1820, had fallen into complete disrepute by the middle of the nineteenth century. The mortality was 80 per cent. and recurrence within a year was the rule.

In 1875 Kocher,<sup>16</sup> applying some of the principles of wound treatment advocated by Lister, introduced his method of tying the rectum above and below the diseased segment and excising it as a closed tube so as to avoid contamination by the bowel contents. In addition, he



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boldly opened the recto-vesical pouch of peritoneum and mobilised the sigmoid colon so that it could be brought down and sutured to the anus. The external sphincter was preserved. Kocher's operation therefore was the prototype of many subsequent attempts to restore the continuity of the bowel and preserve some measure of control. Furthermore, the mortality rate was brought down to the more reasonable level of 20 per cent.

In 1885 Kraske<sup>17</sup> modified Kocher's operation by excising the coccyx together with part of the left margin of the sacrum below the level of the third foramen. This allowed better access to the rectum and permitted removal of the retro-rectal glands. As in the Kocher operation the sigmoid was brought down and sutured to the anus. Hochenegg,<sup>18</sup> a great exponent of the Kraske operation, modified it by introducing his pull-through method for restoring intestinal continuity and preserving sphincter control. In this operation the divided upper segment of bowel was brought down and invaginated through the anal canal, the mucous membrane of which was removed. This procedure has considerable merit and gains added importance from the fact that in the present revival of interest in restoration of bowel continuity, it has been employed not infrequently.

In this country, interest in the surgical treatment of rectal cancer was revived through Sir James Paget, Marrant Baker, Allingham, and later Harrison Cripps. At first only modified Lisfranc operations were performed, but by the turn of the century Harrison Cripps<sup>6</sup> was performing "cuff" resections by the sacral route with restoration of continuity in a certain proportion of cases. Operations devised to retain sphincter control were carried through by Maunsell as early as 1892, and later, ingenious modifications were suggested by Louisa Aldrich-Blake<sup>1</sup> and Sir Charles Ball,<sup>5</sup> though these methods do not appear to have had more than a limited trial.

In 1908 Miles<sup>23</sup> entered the field with his radical abdomino-perineal operation. It was the practical expression of Moynihan's dictum that the surgery of malignant disease was the surgery of the lymphatic system. The chief virtue of the Miles operation was that it permitted ligation of the inferior mesenteric pedicle at a much higher level than was possible in an operation carried out entirely from below. This meant that it offered hope of successful eradication of malignant disease even in cases with high lymph node involvement.

Its high mortality of over 20 per cent. for a time stood in the way of its general acceptance, and the less radical perineal operation, of which the leading exponent was Lockart Mummery,<sup>21</sup> held its own because of its lower mortality rate of under 10 per cent. With better preparation of the patient, and a better appreciation of the principles of fluid and electrolyte balance, together with the introduction of blood transfusion, shock was minimised and the mortality rate was brought down to under 10 per cent. and in some series as low as 5 per cent. Coincidentally the 5-year non-recurrence rate rose to nearly

70 per cent. in Miles's own series. When it is realised that on the continent of Europe at this time the surgeons were obtaining on an average only 17 per cent. of "cures" and many of these calculated on a 3-year non-recurrence rate, the importance of Miles's contribution can be appreciated. Within the past years the percentage of 5-year cures has dropped to round about 50 per cent., as with the better control of shock more and more of the unfavourable cases are being submitted to radical operation.

Nevertheless the permanent abdominal colostomy was never popular with patients, and even during the ascendancy of the Miles operation, attempts to restore intestinal continuity in selected cases were never entirely in abeyance. In 1931 Grey Turner<sup>28</sup> reported a series of 17 consecutive cases in which resection of the rectum by the perineal route with preservation of sphincter control was carried out. Fourteen of these operations were for malignant disease and there was no immediate mortality. Seven patients were alive and well at periods from 5 to 12½ years after operation, and all with satisfactory control. Through the kindness of Professor Grey Turner<sup>29</sup> I have been able to learn the after histories of these 7 patients. Five died without recurrence of malignant disease at periods of from 8 to nearly 26 years after operation. Two are still alive and well at 22 and 26 years respectively after operation.

Grey Turner stressed the fact that this conservative operation was restricted to clinically early cases in which the growth was well localised, and preferably of the papillomatous variety. Such conditions were not met with in more than 5 per cent. of the patients submitted to operation. He also performed a few resections with anastomosis from the abdominal route.

In 1935, C. A. Pannett<sup>25</sup> in this country described his method of abdomino-sacral resection with restoration of continuity, while about the same time Devine<sup>7</sup> of Melbourne reported cases in which he had resected recto-sigmoid growths and restored continuity by operation in stages, the first stage being a transverse colostomy which defunctioned the colon below and lessened the danger of sepsis.

At St Mark's Hospital within the past ten years there has been increasing interest in the possibility of rectal resection with restoration of continuity for high growths not easily felt by the examining finger, and I am indebted to Mr O. V. Lloyd Davies<sup>20</sup> for his kindness in giving me an account of the practice at St Mark's, together with the fruits of his own extensive experience.

The earliest restorative operations, as Lloyd Davies prefers to call them, were carried out by the abdomino-sacral route but were unsatisfactory on account of the frequency of fistula formation. An abdomino-anal technique was then employed, preceded by colostomy in the transverse colon. From the abdominal side the sigmoid and rectum were completely mobilised, the mesenteric vessel tied and the level of viability of the bowel determined. Then from below, the

mucous membrane above the anal canal was brought through the anus, the bowel divided and the rectum pulled through the anus until the level of viable bowel in the sigmoid was reached. Division was made above this level and the anastomosis completed, as in the Mickulicz operation for prolapse. The posterior rectal space was drained through the line of anastomosis. If a fistula formed, it was a blind internal fistula, not troublesome, and this permitted the transverse colostomy to be closed earlier and minimised the danger of stricture. Recently more cases are being done with anastomosis from the abdominal side and without the use either of preliminary colostomy or colostomy at the time of operation. Preparation of the bowel by sulphaphalidine is carried out for five days previous to operation.

In the earlier series of 54 cases, there were 3 deaths, none of them attributable to sepsis, but there was a local recurrence rate of 24.6 per cent. In his present series Lloyd Davies is paying more attention to the irrigation of the rectum below the line of anastomosis with 1 in 1000 perchloride of mercury, as he considers that local recurrence may be due to the implantation of malignant cells from the growth at the time of operation. He also stresses the danger of a second primary tumour and advises regular sigmoidoscopic examination in the post-operative period. In America, restorative resections are having an extensive trial. The only large series is reported by Dixon<sup>8</sup> of the Mayo Clinic who has been carrying through resections with primary anastomosis for growths in the lower sigmoid, recto-sigmoid, and upper rectum for the past 12-15 years. For rectal cases, totalling over 200, the mortality was in the neighbourhood of 12 per cent., but his recent overall mortality, including sigmoidal growths, is only 5.9 per cent. He claims a 5-year non-recurrence rate of 67.7 per cent.

In 1945, Wangenstein<sup>30</sup> reported 22 cases of ampullary rectal resection for carcinoma with restoration of continuity by primary suture from above. He employed an aseptic method of anastomosis, but utilised neither preliminary or complemental colostomy nor preliminary preparation of the bowel with sulphasuccidine. There were two deaths. At the meeting of the American Proctological Association last year Wangenstein<sup>31</sup> reported the follow-up of these cases, together with a later series. Local recurrence was frequent in low-lying lesions, less than 8 cm. from the pectinate line. From 8-13 cm. the operation was unsuitable for large and partially adherent growths, but the results in recto-sigmoid growths compared favourably with those obtained by abdomino-perineal resection, both as regards immediate mortality and long term survival.

Since 1939, Wayne Babcock<sup>3</sup> and Bacon<sup>4</sup> have been employing an abdomino-perineal operation in which continuity is preserved by a modified pull-through procedure. Wayne Babcock reports 44 cases with 2 deaths, but sphincter control was not complete in about 40 per cent. of the patients. In his most recent communication Bacon appears to be reverting to a primary suture method carried out entirely from the abdomen.



ANATOMICAL CONSIDERATIONS IN RELATION TO RECTAL RESECTION WITH RESTORATION OF CONTINUITY (Fig. 4).—The difficulties associated with anastomosis after rectal resection arise mainly from the precarious blood supply and from the absence of a serous coat in the lower rectal segment. The superior hæmorrhoidal artery is the main blood supply to the rectum and when it is ligatured the remaining lower segment of sigmoid is nourished by the marginal artery through the left colic or upper sigmoid branches. There is no marginal artery to the rectum such as exists throughout the remaining large intestine. The middle hæmorrhoidal artery is a vessel of variable size running in the lateral ligaments and is distributed to the anterior part of the rectum above the levator attachment. The inferior hæmorrhoidal artery is distributed to the posterior part of the bowel below the levator attachment. There is an additional blood supply to the rectum from the middle sacral artery, and this is given off opposite the last piece of the sacrum. Where the lower margin of the tumour is higher than 5 inches from the anus, it is possible to secure adequate mobilisation of the bowel from above and yet preserve the middle hæmorrhoidal blood supply. Under these circumstances the remaining rectal segment is well vascularised and an anastomosis heals without fistula formation. A tumour, whose lower margin is less than 5 inches from the anus will require mobilisation of the rectum so far in a downward direction that the blood supply from middle hæmorrhoidal and middle sacral arteries must be sacrificed. Anastomosis in these cases is followed very frequently by fistula formation.

In my own practice during the past three years, rectal resection with primary anastomosis was carried out in every case in which the operation was considered feasible, namely in freely movable growths whose lower margins were at least 2 inches above the ano-rectal ring.

*The Preparation of the Patient.*—In the earlier cases no preliminary transverse colostomy was done. The patient was given a high protein, high carbohydrate and low fat diet. Only paraffin was employed for bowel lubrication and enemas were given every second day. Succinylsulphathiazole was given for 5 days previous to operation in doses of 5 tablets ( $2\frac{1}{2}$  gm.) every 4 hours. Low residue diet was given during the 24 hours preceding the operation, and during this time teaspoonful doses of paregoric were given every 4 hours to ensure that the bowel contents were solid, a point of some importance if soiling is to be avoided with a "no-clamp" technique.

*The Operation.*—A catheter is passed and kept in position, for the operation may last two hours and it is important that the bladder be kept completely empty if visualisation of the deeper part of the pelvis anteriorly is to be satisfactory. In the operating room the rectum below the growth is carefully cleansed, dried and lightly packed with gauze wrung out of tincture of iodine. A high Trendelenburg position is employed and the abdomen is opened either by a mid-line incision or by a long curved incision in the left iliac fossa. The preliminary

steps are similar to those in the abdomino-perineal procedure. Peritoneal flaps are fashioned lateral to the colon, and the sigmoid colon and lower descending colon are extensively mobilised. The superior hæmorrhoidal vessels are ligated just above the sacral promontory. Some surgeons advise transillumination of the mesentery to ensure that the ligature is placed between the sigmoid branches, but I have not found this necessary. The sigmoid colon is divided low enough to allow it to be brought down easily without tension and yet high enough to ensure brisk bleeding from the cut end. The mesentery is then divided and the mobilisation of the lower sigmoid and ampulla of rectum carried out. The rectum is stripped from the bladder and vagina, or from the vesicles and prostate anteriorly, and from the hollow of the sacrum posteriorly. In high-lying growths it is possible to get 2 inches below the growth, preserve the middle hæmorrhoidal artery, and carry out the remainder of the operation entirely from above.

In these cases the gauze is removed from the lower rectum, which is then clamped 2 inches below the growth, and the lower rectum cleansed once more from below and thoroughly dried. The bowel is then cut across and anastomosis completed with interrupted silk stitches. Two rows are employed. The presacral space is drained through an incision in front of the coccyx, and the peritoneal flaps are closed around the bowel so as to reform the pelvic floor. In the majority of cases a rectal tube is passed beyond the anastomosis and fixed by a stitch to the skin round the anus. In the mid-ampullary growths mobilisation has to be carried nearly to the apex of prostate in front, and to the tip of the coccyx posteriorly. The lateral ligaments and middle hæmorrhoidal vessels are divided. If after division of the rectum, the lower segment is too deep to permit of an accurate anastomosis, the operation is completed as a "pull-through" or more often the patient is turned into the left lateral position, an incision made from behind the anus to the lower sacrum, and the coccyx removed. The levator raphe is then split and the mobilisation of the lowest portion of rectum carried out from below. Resection and anastomosis is done from the perineum, which is then closed with drainage. Finally, from the abdominal side the peritoneal flaps are sutured round the sigmoid and the pelvic floor reconstituted.

*Analysis of Cases.*—Within the past three years, 19 patients with carcinoma of the rectum have been treated by resection with restoration of continuity. This is about half the total number of patients submitted to operation during this period. These operations are summarised in Table II. They fall into five groups.

- (1) Resection and primary anastomosis entirely from above—11 cases.
- (2) Abdomino-sacral resection with anastomosis—3 cases.
- (3) Abdomino-sacral mobilisation with Hochenegg "pull-through"  
—3 cases.
- (4) Sacral "cuff" resection with anastomosis—1 case.
- (5) Per-anal resection and anastomosis—1 case.

TABLE II  
Results in 19 Patients undergoing Recto-sigmoid and Ampullary Rectal Resection

	Sex Age.	Distance of Lesion from Anus.*	Character of Lesion.	Operation Performed.	Supplementary Colostomy.	Complications.	Sphincteric Function.	Observations.
1	M. 73	12 cm.	Polypoid B grade 2	Primary closed Anastomosis (Suture from above)	No	Urinary obstruction required Prostatectomy	Good	Well after 3 years
2	M. 69	13 cm.	B grade 3	Primary closed Anastomosis. (Suture from above)	No	None	Good	Well after 3 years
3	F. 58	10 cm.	B grade 2	Primary closed Anastomosis. (Suture from above)	No	Ileus P.O. vomiting. Pulmonary oedema	...	Died 12th day post-operatively. Overdosage intravenous fluid
4	M. 70	12 cm.	B grade 3	Primary closed Anastomosis. (Suture from above)	No	Diarrhoea for one month	Good	Well after 18 months
5	M. 70	9 cm.	A grade 2-3	Hochenegg pull-through	No	Pneumonia.	...	Died 15th day post-operative
6	M. 51	10 cm.	C grade 2	Hochenegg pull-through	No	Wound disruption None	Good	Hepatic metastases present at operation. Died after one year. Pathologist reported end of resection below lesion has not cleared area of local invasion
7	M. 56	9 cm.	C grade 4	Primary closed Anastomosis. (Suture from above)	No	Adherent small bowel diffusely invaded and excised. Abdominal Fistula	Fair	Local recurrence at line of anastomosis after one year

CARCINOMA OF THE RECTUM

CARCINOMA OF THE RECTUM									
8	M. 48	12 cm.	B grade 2	Primary closed Anastomosis. (Suture from above)	No	Bladder involved. Partial cystectomy. Ileus for 9 days	Good	Well after one year	
9	M. 48	13 cm.	B grade 2-3	Primary closed Anastomosis	No	Diarrhoea. Incontinence one month. Urinary retention one month. Fistula closed in 3 weeks	Good	Well after one year	
10	F. 54	8 cm.	B grade 3	Pull-through	No	None	Fair	Local recurrence within one year. Abdomino-perineal operation performed	
11	F. 70	14 cm.	C grade 2	Primary closed Anastomosis. (Suture from above)	No	Fistula closed in 2 weeks	Good	Going down-hill after 18 months	
12	F. 75	10 cm.	C grade 2	Sacral excision with end to end Anastomosis	No	Fistula. Stricture	Good	Well	
13	F. 64	9 cm.	A grade 2	Abdomino-sacral Anastomosis	Yes	Fistula. Stricture	Good	Stricture responding to treatment	
14	F. 61	10 cm.	B grade 2	Abdomino-sacral Anastomosis	Yes	None	Fair	May require colostomy	
15	F. 52	12 cm.	B grade 2	Primary closed Anastomosis. (Suture from above)	Yes	None	Good	Well	
16	M. 55	8 cm.	A grade 2	Anastomosis through Anal Canal	No	Anastomosis gave way on 7th day	Good	Well	
17	M. 64	9 cm.	C grade 3	Resection with pull-through	Yes	None	Good	Well	
18	M. 50	13 cm.	B grade 2	Primary closed Anastomosis. (Suture from above)	No	Diarrhoea one week	Good	Well	
19	F. 68	14 cm.	B grade 2	Primary closed Anastomosis. (Suture from above)	No	None	Good	Well	Secondary Colostomy. Died within a year from Hepatic Metastases

\* pectinate line.

**RECTAL RESECTION WITH ANASTOMOSIS FROM ABOVE.**—This operation was carried out in cases of carcinoma of the recto-sigmoid and upper third of the rectum, where the lower margin of the growth did not reach lower than 5 inches from the anal margin. In only 3 cases of this group, was complementary colostomy done. There was one death due to ileus with vomiting, and subsequent over-use of intravenous fluids. In this case too much reliance was placed on the indwelling gastric tube and it is probable that the patient could have been saved by an early colostomy. In point of fact, ileus with distension due to a low-grade posterior rectal space infection has been the only important complication in this group. Fistula formation did not occur, and the only other complications were diarrhoea, which might last from one to two weeks, and retention of urine in the male cases. These patients, with one exception, all remained well, though the period is still too short to make a final assessment on this point. Sphincter control has been perfect in all patients.

**ABDOMINO-SACRAL RESECTION WITH RESTORATION OF CONTINUITY BY SUTURE OR BY "PULL-THROUGH."**—This operation was carried out on 6 patients, in whom the lesion might be classed as mid-ampullary. The lower margin of the growth lay between 3 and 5 inches from the anus, and was too low for the operation to be completed entirely from the abdominal route. One patient in this group, a frail hemiplegic, died from pneumonia and wound disruption. The remainder all developed fistulas, posterior space infection was more severe, and convalescence prolonged. There was local recurrence at the suture line in two patients within a year of operation, one of whom was submitted to a subsequent abdomino-perineal resection with colostomy. The other patient with recurrence had a grade iv carcinoma and further operation was not considered worth while.

In both these patients the anus remained patulous and sphincter control was imperfect. As this existed right from the time of operation, it was probably due to sacrifice of the internal sphincter and some nerve damage to external sphincter rather than to recurrence of malignant disease.

Another patient in whom the operation was completed as a "pull-through" was a failure from the anastomosis point of view. This was due to necrosis of the lower segment of sigmoid, which was under slight tension. It is one of the drawbacks of the "pull-through" operation that it requires a long voluminous sigmoid. The remaining two patients of this small group both developed severe stricture at the line of anastomosis. One is proving amenable to treatment by regular dilatation, but the other, in whom the stricture is associated with recto-vaginal fistula, will probably require a colostomy.

**LOCALISED RESECTION ENTIRELY FROM BELOW.**—A localised "cuff" resection with anastomosis was carried out by the perineal route in a very frail old patient with an early localised growth of the mid-ampulla. This is the operation described by Grey Turner, and

though the ideal indications for its performance are rarely encountered, it is a very satisfactory and worth-while procedure. The other operation carried out entirely from below was in a patient with a localised papillomatous growth of the lower ampulla. In addition, a mild prolapse was present so that through the dilated anus it was easy to bring the growth outside and amputate the segment of bowel containing the tumour, the operation being completed as in the Mikulicz operation for prolapse. Such an operation has no claim to be regarded as radical, though the fact that the bowel prolapses easily is confirmation that the growth is early and superficial. The sole recommendation for this operation is its ease of performance and its safety.

CONCLUSIONS.—In the past, attempts to attain the surgical ideal of removal of a carcinoma of the rectum with restoration of continuity have been bedevilled by a high mortality rate, and in the survivors by a high early recurrence rate. The high operative mortality was due in the main to shock, necrosis at the suture line and sepsis, while early recurrence was due to the restricted type of operation performed.

Within the past few years, chiefly as a result of advances in the control of shock, and in the reduction of the bacterial content of the large bowel through the use of sulphonamide drugs, resection of the colon for carcinoma with primary anastomosis has been carried out with a very low mortality. This has raised hopes that a similar procedure might be successful in the rectum, though the latter, with peritoneum covering only the anterior portion of its upper third and with no marginal artery, presented a more difficult problem than the rest of the large intestine. In addition, an impetus towards the salvage of the sphincter mechanism was provided by pathological studies which confirmed the very limited longitudinal spread of carcinoma of the rectum beyond the visible margin of the growth, and also showed that lymph node involvement was only rarely met with below the level of the growth. When it did occur, it was only in advanced cases where the upward lymph channels were blocked and where cure by any operation was unlikely.

The present series comprised 19 patients who were submitted to resection of the rectum for carcinoma with restoration of continuity. These 19 patients represented half the total patients submitted to operation for rectal cancer during this period. Wisdom after the event has shown that this is far too high a percentage of cases suitable for a restorative operation, but some faulty selection of cases has at least served to throw the merits and shortcomings of the operation into bolder relief.

There were two deaths from operation in the series, a mortality of 10.5 per cent., and one death could probably have been avoided by a timely colostomy. In a word, the operative mortality is comparable to that of the abdomino-perineal operation, and this is confirmed by the series of 18 cases recently published by E. G. Muir<sup>21</sup> apparently

without mortality, and by the unpublished series of 53 cases by Lloyd Davies, with only three deaths.

The most satisfactory type of operation is resection and primary anastomosis carried out entirely from within the abdomen, and this is suitable for growths of the recto-sigmoid and uppermost portion of the rectum, the lower margins of which do not reach below 5 inches from the anal margin. This ensures that the rectum can be cut across at least 2 inches below the lower margin of the growth, and both internal and external sphincters are spared, so that sphincter control is perfect. In this series of recto-sigmoid and upper ampullary resections, neither fistula nor stricture were met with, and there has been no instance of local recurrence, though the longest period which has elapsed since operation is only three years.

The mid-ampullary and lower ampullary growths are unsuitable for conservative operations, or as Lloyd Davies prefers to call them, restorative operations. These growths are situated between 3 and 5 inches from the anal margin. Some of these cases can be dealt with entirely from the abdomen, but such operations are technically difficult and it may not be easy to cut across the bowel sufficiently far below the lesion to ensure that one is beyond the limits of extension of the disease. Such cases may require completion by the sacral route or by a "pull-through" procedure. In my experience these cases have proved unsatisfactory. The blood supply from the middle hæmorrhoidal and middle sacral arteries is sacrificed, fistula formation is the rule, and stricture formation is very liable to occur. Again, in these anastomoses carried out at a low level the internal sphincter is sacrificed and the patient is dependent entirely on the external sphincter. This means that control is not perfect.

In low resections completed by the sacral route some division of the levator ani is unavoidable, and as the inferior hæmorrhoidal nerves run on its lower surface (Fig. 5), they are liable to damage and the external sphincter may remain patulous. Though in these cases a certain amount of control is obtained, it is little better than that met with in a perineal colostomy which has developed some regularity of action.

Most important of all, in the 6 cases belonging to this group, local recurrence within a year has been met with in 2 cases. Whether this is the result of lateral lymphatic spread or spread by direct continuity seems merely of academic importance. The practical point is that the nearer the line of resection approaches the lower attachment of the levator ani, the more difficult does it become to deal adequately with the lateral zone of spread without sacrificing the levator muscle and the sphincter apparatus. Lloyd Davies considers that some cases of recurrence may be due to local implantation of malignant cells at the time of operation and his present technique is designed to minimise this danger. While the precautions he has advised should be followed, it is unlikely that local implantation of malignant cells at the time

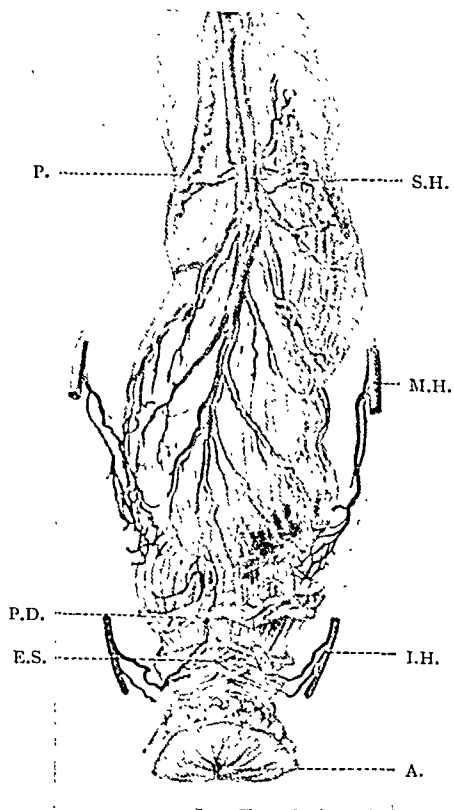


FIG. 4.—Blood supply of rectum (after Sir Charles Ball).

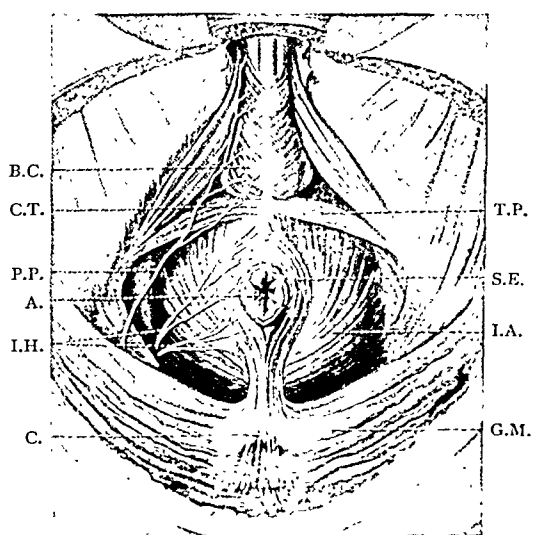


FIG. 5.—Anatomy of perineum showing close relationship of inferior hæmorrhoidal nerves to lower surface of levator ani.





of operation is the commonest cause of recurrence in the region of the suture line.

Two patients of this small mid-ampullary group developed severe stricture at the suture line. In both cases a fistula was present and there was a prolonged inflammatory reaction. One patient is responding satisfactorily to treatment, but the other, in whom the stricture is associated with a persistent recto-vaginal fistula, will probably require a colostomy and must be regarded as a failure from the standpoint of restoration of continuity.

With only one exception, the resections in this series have been carried out without a preliminary transverse colostomy. Preliminary transverse colostomy adds a measure of safety to the main procedure, but has the disadvantage that the defunctioned colon below the colostomy becomes smaller, and at the second operation there is disproportion between the narrow sigmoid and the wide ampulla. Lloyd Davies overcomes this by slitting the antimesenteric margin of the sigmoid, and Muir, by oblique section of the bowel. This difficulty has been largely avoided in the present series and in addition the tendency to stricture is minimised, for the anastomosis is kept dilated by the solid faecal mass from an early period after operation. A good case can be made out for a compromise in which a transverse colostomy is done at the time of the main operation. After resection of the rectum with restoration of continuity, ileus and abdominal distension may be very prominent. A colostomy at the time of resection makes the convalescence smoother and adds safety should anything go wrong at the suture line. A simple loop colostomy is sufficient and is easier to close than the Devine type.

In suggesting that restorative operations for carcinoma of the rectum should be confined to growths in the recto-sigmoid and uppermost portion of the rectum, the question arises as to what proportion of all rectal growths are found in this region. From an analysis of 1401 cases Bacon<sup>4</sup> estimates that about 30 per cent. of all rectal cancers are situated at this level, and rather less than this percentage of cases should be suitable for resection with restoration of continuity and with results as regards non-recurrence comparable with those obtained by the standard abdomino-perineal procedure. In 1938, Dukes and Lloyd Davies,<sup>32</sup> from a study of 400 consecutive specimens from radical excisions of the rectum concluded that in nearly a third of the cases a conservative excision would have been successful, and that in another third the extent of the growth precluded successful resection by any method. Thus, half the genuinely operable cases could have been successfully dealt with by conservative resection. This, however, is being wise after the event, and to select the favourable cases for conservative operation will present the surgeon with a most difficult clinical problem. In the main he should avoid conservative operation in growths of the mid-ampulla, in large growths tending to adhesion, in growths in relatively young subjects, and in growths which biopsy

has shown to be of a high grade of malignancy. In all doubtful cases the standard abdomino-perineal operation should be preferred.

It is yet too early to state the final place of restorative operations in the treatment of carcinoma of the rectum, but at least sufficient experience has been gained and sufficient time has elapsed to reveal some of the shortcomings of the operation when applied to unsuitable cases. In the words of the Duke of Wellington, "We have learned what not to do and that is always something."

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At a Meeting of the College held on 1st February, with Dr W. D. D. Small, C.B.E., in the Chair, the following were elected to the Fellowship :—  
**Royal College of Physicians of Edinburgh**  
 R. G. McInnes (Oxford), K. M. Morris (Edinburgh),  
 W. J. Burns (Edinburgh).

The Diploma of Membership was conferred upon the following :—

W. G. Greene (Chester), F. O'D. Finigan (London), R. Natarajan (Deolali, India), Siva R. K. Padmavati (Coimbatore, India), J. M. Barber (London), F. G. Pattrick (King's Lynn), A. M. Merriweather (Bechuanaland), R. E. Beamish (Winnipeg), R. P. Gillespie (Edinburgh), S. P. Hall-Smith (Hove), J. R. Mackenzie (Carlisle), I. H. Stokoe (Edinburgh), R. M. Marquis (Edinburgh), D. H. Reilly (Quebec), J. Williamson (East Kilbride), A. W. B. Cunningham (Edinburgh), R. G. Mitchell (Edinburgh), Alwyce B. Gordon (Sydney), R. A. Bustamante (London), G. L. Brinkman (London).

## NEW BOOKS

*The Year Book of Obstetrics and Gynaecology*—1947. Edited by J. P. GREENHILL, M.D. Pp. 590, with 117 illustrations. Chicago: The Year Book Publishers. Price \$3.75.

This volume retains the essential characteristics of its predecessors. In it is to be found extracts of papers appearing in medical journals published the world over between October 1946 and September 1947. All the important growing points of obstetrics and gynaecology are touched on and the papers are well grouped together.

The feature of this year book, as hitherto, is the editorial notes. These bring together in a critical manner various aspects of the problems under discussion and in general provide a balanced assessment. Many of these notes have entailed considerable thought in their preparation and their usefulness to the reader is enhanced by the inclusion of references. They are most valuable lecturettes.

This year book will be found to maintain the high standard now anticipated in this critical guide to recent literature.

*The British Pharmacopæia* 1948. Pp. xl+914. Price 45s.

The last edition of the *Pharmacopæia* appeared in 1932 and since then a series of seven addenda have tried to keep step with medical advances. The new volume includes most of the material in the addenda and brings the position up-to-date. Deletions include things which have gone out of fashion or have been replaced by more active remedies and there are a large number of valuable introductions. There are no capsules and only five official pills, but a large number of drugs in tablet form. Drugs for giving by injection have been greatly increased since the 1932 edition. Technical information contained in the appendices has also been increased considerably.

The Pharmacopœial Commission and its various committees are to be congratulated on the vast amount of excellent work they have done in the preparation of the new volume.

*Chronic Structural Low Backache*. By R. A. ROBERTS, B.Sc., M.B., D.M.R.E. Pp. viii+105, with 137 illustrations on 46 plates. London: H. K. Lewis & Co. Ltd. 1947. Price 45s. net.

A lucidly written and well-illustrated monograph by a radiologist for the general practitioner, surgeon and radiologist, and taking a definite step forward in reducing

the large number of "Problem Chronic Backaches." It contributes another little known but relatively common pathological condition of the pars interarticularis and emphasises the multiplicity of joints, ligaments, and muscles of the vertebral column where there is a distinct danger of concentrating too much attention on one region such as the intervertebral disc.

The pars interarticularis is the portion of the vertebral lamina between the superior and inferior articular process and the author describes osteoporosis at this site as a sign of chronic structural derangement of the back. Unilateral or bilateral spondylolysis or spondylolisthesis occur as a result of this osteoporosis, and are explained as an hyperæmia from over-strain as in fatigue fractures.

A strong plea is made for recognition that spinal derangement is an important differential diagnosis in anterior disease.

*Principles of Medical Statistics.* By A. BRADFORD HILL, D.SC., PH.D. London : The Lancet. 1948. Price 10s. 6d. net.

This small book has evidently supplied a need in medical work for the third edition which appeared in 1942 has twice had to be reprinted. Professor Hill has now found time to undertake revision and has taken the opportunity to include some new matter in the present edition. The principal additions are a more detailed discussion of the tabulation of a frequency distribution and of diagrams derived from it; a new chapter on the calculation of averages, and several other sections have been extensively modified. The effect of these changes should be to make the book more useful to those engaged in preventive medicine.

*Sir Frederick Banting.* By LLOYD STEVENSON. Pp. 446, illustrated. London : William Heinemann (Medical Books) Ltd. 1947. Price 25s.

The story of insulin has often been told, and all the world knows how this discovery has changed the entire outlook of the diabetic patient. The details of the career of its discoverer are much less familiar, and they were well worth recording, as Sir Frederick Banting was not only a great scientist, but also a great personality, one of Canada's most gifted sons, who inspired a whole generation of young scientists. Dr Stevenson has performed his task as biographer with great success. The first half of the book is fascinating; the early days, the first idea, the laborious research, the discovery, the world wide fame—all form an entrancing narrative which grips the reader. His interest may flag in the next three chapters, largely composed of extracts from the diaries and letters of Dr and Mrs Banting, but his attention will be recaptured in the concluding chapters which give a clear picture of Banting's later achievements and of his service in the Second World War, culminating in his death in an aeroplane crash in February 1941.

Banting inspired enthusiasm in others. He took a share in many careers. He left a shining example of success achieved in the face of many difficulties. Such a life has many lessons. Here is a story worth pondering, simply and beautifully portrayed.

*No Retreat from Reason.* By ALFRED E. COHN. Pp. xi+279. New York : Harcourt, Brace & Co. 1948. Price \$3.50.

Dr Cohn of the Rockefeller Institute for Medical Research is an author of repute; his *Medicine, Science and Art* and *Minerva's Progress* have already established his claim to fame. The present volume contains a further selection of his erudite essays. The subjects dealt with cover a wide range. There are biographic essays on John Wyckoff and Simon Flexner, an account of the development of the Harveian circulation and articles on the changes in the attitude of the public towards medicine, and on several other matters.

Dr Cohn is a master of language and writes with great insight and the result is a very attractive book, which can be thoroughly recommended to the medical profession.

*Gastritis.* By R. SCHINDLER, M.D., F.A.C.P. Pp. xi+462, with 96 illustrations. London: William Heinemann (Medical Books) Ltd. 1948. Price 50s. net.

Dr Schindler, a pioneer in gastroscopy, writes authoritatively from a long experience of gastric disorders. He begins by describing the history of the subject, then devotes several pages to definitions so that there can be no doubt as to what is being discussed. Some sixty pages are allotted to normal histology and gross and microscopic pathology. In the clinical section all varieties of gastritis are discussed in considerable detail and attention is given to the association with various other disorders.

As an appendix the histories of fifty-five selected cases are given together with an excellent series of illustrations, mostly histological but including two coloured plates of gastroscopic appearances.

This excellent monograph is likely to become a standard book of reference on the subject.

*The Medical Annual.* Edited by Sir HENRY TIDY and A. RENDLE SHORT. Pp. 464, with 43 plates and numerous illustrations. Bristol: John Wright & Sons Ltd. 1947. Price 25s.

The new *Medical Annual* follows the usual character of earlier volumes and contains abstracts of recent papers in every field of medical work. The articles are highly informative and give the essence of the most valuable papers that have appeared. Penicillin, streptomycin and the newer sulphonamides receive prominence. There is an interesting article on Tracer substances and their uses. Professor Crew has contributed an article on "Social Medicine" a subject which appears for the first time in the *Annual*. The present volume maintains the high traditions of the past and should be in the hands of every practitioner of medicine.

*Sex Power in Marriage.* By E. W. HIRSCH, B.S., M.D. Pp. xi+218. Chicago: Research Publications of Chicago. 1947. Price \$3.

This book, primarily for the layman, has been written by a medical man who has specialised in this field for many years. He treats the subject frankly and fully and in a thoroughly scientific manner. The subject is one which receives scant attention in the medical curriculum, and the practitioner faced with problems of this sort might derive much help from this little book.

*Handbook of Fractures.* By DUNCAN EVE. Pp. xi+263, with 129 illustrations. London: Henry Kimpton. 1947. Price 25s.

In his preface the author states that the methods discussed in this book are the gleanings from more than forty years of trials and errors in the field of fracture work; that to prevent confusion he has only described the methods he has found most satisfactory, and that in the book lengthy discussion of the manner of injury together with the signs and symptoms of fractures are either shortened or waived in favour of emphasis upon details of treatment. The plan adopted detracts from the value which a book, based on such ripe experience, should have. It lacks the critical appraisement that would make it of use to the specialist, and the details of the signs and symptoms, which would help the less experienced in diagnosis, are missing. The author depends largely on traction for securing a reduction of fractures. The very successful method of angulation is not considered. The illustrations are well reproduced.

*The Secret Instrument.* By WALTER RADCLIFFE. Pp. xvi+83, with 23 illustrations. London: William Heinemann (Medical Books) Ltd. 1947. Price 10s. 6d.

This is the story of the midwifery forceps told by a doctor who practises in "the very cradle of operative midwifery"—the county of Essex. There in the old home of Dr Peter Chamberlen were discovered, in 1813, the instruments that had lain hidden away for over one hundred years. The author gives an account of the



Chamberlen family and discusses the possible ways in which the carefully guarded family secret eventually leaked out to the world. More credit is claimed for the part played by three Essex doctors of the eighteenth century who publicised and improved the obstetric forceps.

The author has added life and interest to his narrative by relating it to a background of contemporary social history. Much information has been skillfully welded together and pruned to make this little volume interesting, instructive and readable.

*Cancer of the Breast.* By D. C. L. FITZWILLIAMS, F.R.C.S. Pp. vi+199, with 24 illustrations. London: William Heinemann (Medical Books) Ltd. 1947. Price 25s. net.

This monograph is the second of an experienced surgeon's personal experience on the treatment of patients suffering from carcinoma of the breast. While the author has employed different methods of treatment, such as local removal of the tumour in very early cases, radical operation, etc., a considerable part of the book describes his work in the use of radium, either alone or combined with surgery. He describes in detail the technique which he has used when treating the case with radium alone, but expresses the view that as a general rule he now combines operation and radium as the best way of treating cancer of the breast. It is doubtful if many will agree with this view, the consensus of opinion at the present time being that some form of surgery plus X-radiation is the most effective method of treatment.

A considerable part of the book is taken up with numerous case reports, which, while of interest in themselves, do not help the reader to form a balanced opinion on the merits of the various forms of treatment used. In fact, one feels after perusing the book that it contributes little towards solving the problem of what is the best form of treatment for this disease.

*Psychotherapy—Its Uses and Limitations.* By D. RHODES ALLISON, M.D., M.R.C.P. and R. G. GORDON, M.D., D.S.C., F.R.C.P. Pp. vii+160. London: Oxford University Press. 1948. Price 8s. 6d. net.

At a time when increasing stress is being laid on the significance of the mind in the etiology of disease this book serves a useful purpose in reviewing the place that psychotherapy can play in modern therapeutics. It considers its importance not only in the treatment of the psychoses and psychoneuroses but also in psychosomatic conditions and various organic diseases. There is no doubt that this aspect of treatment tends to be neglected in both hospital and general practice and this book will prove a useful guide to the indications for psychotherapy, and should appeal to a wider public than those more especially interested in mental disease.

The authors also stress the need for students to receive more instruction in this branch of medicine, instruction which would best be carried out at the time of their clinical work.

Finally they make a plea for increased co-operation between the psychiatric worker and those in other branches of medicine so that in these days of increased specialisation the patient does not fall a victim to this trend but, on the contrary, gains fuller and more skilful treatment.

*Chronic Ill-Health Relieved by Drainage of the Para-Nasal Sinuses.* By ROSA FORD, M.B. (LOND.), D.O. (OXON.). Pp. ix+104, with 13 illustrations. London: Henry Kimpton. 1948. Price 6s. net.

As the writer states this is not a comprehensive treatise on sinusitis but a collection of case records of various types of chronic ill-health purporting to show latent sinusitis as the aetiological factor. It is probably true that the last word has not yet been said on the subject of focal sepsis, but many will doubt the inclusion of duodenal ulcer, disseminated sclerosis and coronary embolus, as conditions due to latent sinusitis. It is noteworthy that the most common conditions associated with chronic

sinusitis—namely chronic pulmonary infection and suppuration—are nowhere mentioned in the book.

*The Oculorotary Muscles.* By RICHARD G. SCOBEE, B.A., M.D. Pp. xvi+343. London: Henry Kimpton. 1947. Price 40s. net.

The study of the oculorotary, or extrinsic, muscles of the eyes form a subject of perennial interest and endless controversy. In the present book Dr Scobee goes thoroughly into the many questions involved with the object of providing, in his own words, "a simple but accurate and workable approach to the subject of the oculorotary muscles and their dysfunction." The book is divided into five sections dealing with anatomy and physiology, latent and manifest deviations, diagnosis and treatment and an appendix on the use of the Maddox rod is added. The subject matter is dealt with so fully that the author's good intentions are sometimes overshadowed by wealth of detail even though in some respects a little more would have been welcome. Two chapters are devoted to non-surgical and surgical treatment respectively but orthoptic treatment is not dealt with in detail. The book is well illustrated and the author is to be congratulated on a work which will prove of value and may be confidently recommended to all ophthalmic surgeons who are interested in problems connected with the extrinsic ocular muscles.

*A Primer of Cardiology.* By GEO. E. BURCH, and P. REASER. Pp. 272, with 203 illustrations. London: Henry Kimpton. 1947. Price 22s. 6d. net.

The authors set out to "teach the reader to think of clinical manifestations (in cardiology) in terms of circulatory dynamics and basic physiologic principles" and to form "a habit of thus evaluating all cardiac states." Once the British reader has overcome the resistance engendered by the rather turgid style he will be grateful to find a valuable presentation of modern ideas of cardiovascular physiology and disease and much useful instruction in diagnosis and treatment. It is surprising that although the theory of the renal mechanism in the genesis of congestive failure is discussed there is no mention of cardiac catheterisation and the light which this technique has thrown on the problems of heart failure and the action of digitalis. The emphysema heart is also omitted. The book is profusely and helpfully illustrated by line drawings and diagrams. The appendix includes sample cardiac diets used at the Charity Hospital, New Orleans. They made the reviewer envious of the Louisiana negro.

*Pathology of Tumours.* By R. A. WILLIS. Pp. xxxiii+992, with 500 illustrations and index of 52 pp. London: Butterworth & Co. (Publishers) Ltd. 1948. Price 63s. net.

Here is a British work of outstanding quality. It is incisive, systematic, thoroughly modern, places stress on definition and leaves no reader in doubt of a considered opinion. That does not mean that the author is never himself in doubt on a subject, nor is he in any way averse from clearly expressing it. The book will be a standby to the beginner in oncology or to one who may be isolated from friendly consultation: it will be a supporting authority for all advanced workers. The illustrations are predominantly microscopic, numerous and very carefully selected: none of them is coloured but that is no great handicap to their understanding, for they depict, clearly and instructively, what they are meant to show. As the author bases his well-known work on a foundation of experience, and especially the complete post-mortem examination, a reader may feel assured that the opinions formulated are personal: they are obviously supplemented by very wide reading, which receives specific recommendations. A still more detailed cross indexing would facilitate reference to the text, but as there is abundant space available we confidently expect that successive editions and additions of text or illustration will not require much increase of the volume size or weight. This is a book that is indispensable to a worker on tumour pathology and is, for value, moderately priced.

*Paravertebral Block.* By FELIX MANDL, M.D., F.I.C.S. Pp. xvii+330, with 20 illustrations. London: William Heinemann (Medical Books) Ltd. 1947. Price 32s. net.

This large monograph is based on investigations into the relief of pain, somatic and visceral, conducted by the author during the past twenty-six years in hospitals in Vienna and latterly Jerusalem. The subject is dealt with exhaustively and the accumulated material has much in it of interest to physicians and surgeons. Paravertebral block is well described in respect to the various technical procedures employed, the text being supplemented by a number of clear drawings. Apart from some minor typographical errors there is a particular mistake on page 26 which must be corrected at the earliest opportunity. "Nupercaine" is not the American name for "procaine." These two drugs differ much in chemical structure and greatly in toxicity. An excellent feature is the comprehensive series of references. The latter have been introduced in sections within the chapters in association with the sub-sections, a great convenience to the reader.

*Dermatoses among Gas and Tar Workers.* By WILLIAM DAVID JENKINS, J.P., B.A., M.R.C.S., L.R.C.P. Pp. 54, with 19 illustrations. Bristol: John Wright & Sons Ltd. 1948. Price 25s.

It is unfortunate that the author did not live to see the publication of his monograph in which he describes the various processes in the manufacture of gas and the resulting by-products and indicates the difference in the latter according to whether they are derived from high or low temperature carbonisation. The hazards are then discussed and it is interesting to note that only 20 cases of acute incapacitating dermatitis and 58 cases of non-incapacitating dermatitis occurred in ten years out of a personnel of 6659. It was found that acute dermatitis was more likely to be produced by agents other than tar. Twenty-three cases of epithelioma occurred, it was observed that this condition can occur long after removal from the effects of the irritants. Excellent photographs illustrate the various lesions.

*How to Become a Pharmacist.* By WILFRED A. MUTEHAM, M.P.S. Pp. 120. London: The Actinic Press. 1948. Price 5s. net.

A brief history of pharmacy is followed by much excellent advice on how to become a pharmacist. Having brought the reader so far, the author gives advice on all branches of pharmacy. Emphasis is rightly on the chemist and druggist qualification, and entrants to pharmacy should read and study this book.

*Clinical Ophthalmology, for General Practitioners and Students.* By H. M. TRAQUAIR, M.D., F.R.C.S.E. Pp. xii+264, with 72 illustrations including 8 coloured plates. London: Henry Kimpton. 1948. Price 25s.

The aim of this book is to present ophthalmology in an elementary manner so that practitioners may be better able to advise their ophthalmic patients. The anatomy and physiology of the eye, including physiological optics, are first considered and then the subjective and objective examination of the patient are described. For these examinations no special instruments are required and ophthalmoscopic examination is not touched at all. Particular attention is paid to the diagnosis of the simpler conditions which can be safely handled by the amateur, and the point at which the help of an expert is required is clearly indicated. The illustrations are beautifully reproduced and well chosen. Throughout the author has inserted practical advice regarding common misconceptions and fallacies so that the practitioner can be in a position to answer patients' questions authoritatively. This book can be cordially recommended to medical practitioners.

*British Journal of Plastic Surgery*—vol. I, part 1. Edited by A. B. WALLACE, M.Sc., F.R.C.S.ED. Pp. 72, illustrated. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 42s. annually.

In these difficult days, we welcome this new journal, the official publication of the British Association of Plastic Surgeons. It is hoped that this highly specialised journal will do much to advance this branch of surgery by stimulating interest and by recording new techniques and the results to be obtained.

The present number contains articles on the repair of the male urethra, pollicisation of the index finger, syndactyly and the treatment of lymphœdema. The journal is beautifully produced, excellently illustrated and is a splendid example of British craftsmanship. Four numbers are to be issued in the year and considering the high standard of the articles and the technical quality of the printing and illustrating the journal is excellent value.

*Sex Fulfilment in Married Women.* By HELENA WRIGHT, M.B., B.S. Pp. 97. London: Williams & Norgate. 1947. Price 5s. net.

Dr Wright has been specially interested in the question of sex education for women and has already written two books on the subject. The present volume continues and amplifies the theme of "The Sex Factor in Marriage." It contains information which should be of the greatest help to practitioners of medicine.

## NEW EDITIONS

*Recent Advances in Surgery.* By HAROLD C. EDWARDS, C.B.E., M.S., F.R.C.S., Third Edition. Pp. vii+437, with 131 illustrations. London: J. & A. Churchill Ltd. 1948. Price 24s.

This is a volume that is long overdue, no less than nineteen years having elapsed since the second was published. Now that it has arrived it is assured of a warm welcome, for the author, ably assisted by several distinguished collaborators, has presented an up-to-date review of the present position of surgery. A comparison between the contents of the present volume and those of the two early editions is sufficient to show the remarkable advances that have been made in the past twenty years. Naturally all aspects of surgery are not dealt with and some subjects are treated more fully than others, but, taken all over, the difficult task of presenting a general review of the present position in such a rapidly advancing subject has been very efficiently done. This book should prove invaluable to all surgeons—general and specialist alike.

*An Introduction to the Principles and Practice of Homœopathy.* By CHARLES E. WHEELER, M.D., B.S., B.Sc., and D. KENYON, M.B., CH.B. Third Edition. Pp. viii+371. London: William Heinemann (Medical Books) Ltd. 1948. Price 21s. net.

Homœopathy claims to be an addition to existing therapeutic resources, and whenever a physician has already such aids as he trusts he will not look beyond them. The subject has for so long been cold shouldered by the profession that it is inevitable that a busy practitioner should hesitate to undertake the study which homœopathy undoubtedly demands before it can be judged fairly. The authors appeal to the profession to give the system a trial.

The first part of the book gives an account of the principles on which homœopathy is based and the rest of it is devoted to description of the various remedies and the methods of employing them.

*Hernia.* By LEIGH F. WATSON, M.D., F.I.C.S. Third Edition. Pp. 732, with 323 illustrations. London: Henry Kimpton. 1948. Price 67s. 6d. net.

This book is a veritable encyclopædia and is a work of considerable magnitude. Every possible sort of hernia is described, even "Hernia into the Broad Ligament." The illustrations form the most striking feature of the book. They are numerous and excellent. The various treatments are described with great care and with the utmost attention to detail. This is most welcome and greatly enhances the value of the work. The author devotes no less than five whole chapters to describe treatment by injection. This method of treatment appears to have found more favour in America than it has in this country. It is of interest also that after operative treatment for hernia patients are encouraged soon to get up and walk. Much of the historical material could have been omitted; however, the full and careful anatomical descriptions, which are so essential, are most helpful. The last chapter on industrial hernia completes a most comprehensive book on the subject.

*Textbook of Anæsthetics.* By R. J. MINNITT, M.D., D.A., and JOHN GILLIES, M.C., M.B., F.R.C.S.E., D.A. Seventh Edition. Pp. vii+568, with 229 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 30s. net.

The subject of anæsthesia has made such remarkable advances in recent years that an authoritative textbook on the subject is a necessity. This outstanding work covers the whole field in a thorough manner. The present edition contains new matter on curare and on legal aspects of anæsthesia and also on regional analgesia. Many new illustrations have also been included.

This standard work should continue to maintain its well-deserved reputation.

*Diseases of the Eye.* By Sir JOHN HERBERT PARSONS, C.B.E., D.SC., F.R.C.S., F.R.S., and Sir STEWART DUKE-ELDER, K.C.V.O., M.A., D.SC., PH.D., M.D., F.R.C.S. Eleventh Edition. Pp. vii+732, with 21 plates and 368 text-figures. London: J. & A. Churchill Ltd. 1948. Price 30s. net.

Since the last edition of this book in 1942 the advent into established clinical practice of the sulphanilamide group of drugs and more particularly of penicillin has necessitated the revision of a great number of the infective diseases of the eye. Other advances, notably in the field of neurology and pathology have been reviewed. The book maintains in every way its high standard and is to be strongly recommended to all interested in this subject.

*The Anatomy of the Eye and Orbit.* By EUGENE WOLFF. Third Edition. Pp. viii+440, with 323 illustrations, including 24 in colour. London: H. K. Lewis & Co. Ltd. 1948. Price 45s.

For the third edition of this well known and deservedly popular book the text has been revised and more than 80 new illustrations have been added. Among other valuable additions are details of the retinal capillaries and the central connections of the visual path. The illustrations are of a high order though some of the coloured photomicrographs show a slight lack of definition. A valuable chapter on comparative anatomy and an excellent index complete the book. A minor fault is slight inconsistency in anatomical terminology, both lateral and external rectus, for example, being included in the index in different places. One notices also the absence of any reference to differentiation between tract and radiation hemianopia on an anatomical basis. Such matters can be remedied in future editions which will certainly be called for. The book is beautifully got up, fascinating to read and ophthalmologists will be grateful for it to both publisher and author. It may safely be predicted that it will find a place on the bookshelf of every ophthalmic surgeon.

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| ANDREWS, G. W. S., M.B., B.S.(LOND.), and MILLER, J., B.S.C.(LOND.). Penicillin and other Antibiotics. . . . .   | (Todd Publishing Group Ltd., London                    | 7s. 6d. net.          |
| BAILEY, HAMILTON, F.R.C.S., F.A.C.S., F.I.C.S., F.R.S.E., and LOVE, R. J. MCNEILL, " . . . . .   | F.R.C.S., F.I.C.S. A Short Practice of Surger. . . . . | 5 parts.              |
|  | Ltd., London)  | £2, 12s. 6d. the set. |
|  |  | Not sold separately.  |
| BAILEY, HAMILTON, F.R.C.S., F.A.C.S., F.I.C.S., F.R.S.E. Demonstrations of Physical Signs in Clinical Surgery. Part IV. Eleventh Edition.  | (John Wright & Sons Ltd., Bristol)                     | 8s. 6d. per part.     |
| BEATTIE, J. MARTIN, M.A., M.D., D.S.C., M.R.C.S., L.R.C.P., and DICKSON, W. E. CARNEGIE, M.D., B.S.C., F.R.C.P.(EDIN.). A Textbook of Pathology. General and Special. Volumes I and II. New Fifth Edition. | (William Heinemann (Medical Books) Ltd., London        | £8, 8s. net the set.  |
| BERNHHEIM, BERTRAM M., M.D. A Surgeon's Domain.  | (The World's Work (1913) Ltd., Surrey)                 | 9s. 6d. net.          |
| BIGGART, J. HENRY, C.B.E., M.D., D.S.C. Pathology of the Nervous System. Second Edition. . . . .   | (E. & S. Livingston Ltd., Edinburgh)                   | 21s. net.             |
| BOGERT, B. JEAN, PH.D. Nutrition and Physical Fitness. Fifth Edition.  | (W. B. Saunders Company, London)                       | 21s.                  |
| Brompton Hospital Reports. Vol. XVI 1947.  | (Gale & Polden Ltd., Aldershot)                        | 10s.                  |
| CADE, Sir STANFORD, K.B.E., C.B., F.R.C.S., M.R.C.P. Malignant Disease and its Treatment by Radium. Volume II. Second Edition.   | (John Wright & Sons Ltd., Bristol)                     | 52s. 6d.              |

- CLARK-KENNEDY, A. E., M.D., F.R.C.P. Medicine. Volume II. Diagnosis, Prevention and Treatment. (*E. & S. Livingstone Ltd., Edinburgh*) 25s. net.
- Collected Papers of The Mayo Clinic and The Mayo Foundation. Volume XXXIX, 1947. (*W. B. Saunders Company London*) 63s.
- COPPER, A. C., M.D. An Introduction to Clinical Orbitonometry. Published by—*H. E. Stenfort Kroese's Uitgevers-Mij N. V. Leiden* Paper 11s. 6d. Obtainable from—*H. K. Lewis & Co. Ltd., London* Cloth 14s. 6d.
- COWAN, ALFRED, M.D. Refraction of the Eye (*Henry Kimpton, London*) 27s. 6d. net.
- CRILE, GEORGE, JR., M.D., F.A.C.S. Practical Aspects of Thyroid Disease. (*W. B. Saunders Company, London*) 30s.
- CURRAN, DESMOND, M.B., F.R.C.P., D.P.M., and the Late GUTTMANN, ERIC, M.D., M.R.C.P. Psychological Medicine. Third Edition. (*E. & S. Livingstone Ltd., Edinburgh*) 12s. 6d. net.
- Edited by CONYBEARE, Sir JOHN, K.B.E., M.C., D.M.(OXON), F.R.C.P. Textbook of Medicine. By various authors. Ninth Edition. (*E. & S. Livingstone Ltd., Edinburgh*) 30s. net.
- Edited by DUNLOP, D. M., B.A.(OXON), M.D., F.R.C.P.(EDIN.), F.R.C.P.(LOND.), DAVIDSON, L. S. P., B.A.(CAMB.), M.D., F.R.C.P.(EDIN.), F.R.C.P.(LOND.), M.D.(OSLO), and MCNEE, J. W., D.S.O., D.SC., M.D.(GLAS.), F.R.C.P.(EDIN.), F.R.C.P.(LOND.). Textbook of Medical Treatment. Fifth Edition. (*E. & S. Livingstone, Ltd., Edinburgh*) 35s. net.
- FRIEL, A. R., M.D.(UNIV. DUB.), F.R.C.S.I. Zinc Ions in Ear, Nose, and Throat Work. (*John Wright & Sons Ltd., Bristol*) 5s. 6d.
- HERBUT, PETER A., M.D. Surgical Pathology. (*Henry Kimpton, London*) 60s. net.
- JOSLIN, ELLIOTT P., M.D., SC.D. Diabetic Manual for the Doctor and Patient. Eighth Edition. (*Henry Kimpton, London*) 12s. 6d. net.
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The Transactions  
of the  
Edinburgh Obstetrical Society

SESSION CI.—1948-1949



AT a Meeting of the Edinburgh Obstetrical Society, held on 10th November 1948, with the President, Dr E. Chalmers Fahmy, in the Chair, the following were elected Office-Bearers for Session 1948-49.

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# The Transactions of the Edinburgh Obstetrical Society

## CAUDAL ANALGESIA FOR THE RELIEF OF PAIN IN LABOUR

By A. F. ANDERSON, M.B., Ch.B., F.R.C.S., M.R.C.O.G.

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University of Edinburgh

### ANATOMY AND PHYSIOLOGY

IT should be understood at the outset that caudal analgesia is a method employing nerve block of extra-dural type. Epidural and peridural are other names for the same thing. The term "caudal" refers to the approach to the extra-dural space not to the extent of analgesia. The method is not, and in fact must not be, spinal block with tapping of the subarachnoid space.

The extra-dural space extends from the foramen magnum to the sacral hiatus, cushioning the spinal cord from the ligaments and periosteum of the vertebral canal. At the sides, where the nerves leave by the intervertebral foramina, this cushion of fatty connective tissue is continued to the paravertebral space and fluid injected into one, readily escapes into the other.<sup>1</sup> The dura mater extends with the nerve roots to fuse with the nerve sheath at or about its formation from the two roots.

In the average subject, the dural sac is said to end at the middle third of the second sacral vertebra, but about 40 per cent. may reach a lower level, nearer an inquisitive needle coming up from below.<sup>2</sup> Put a more practical way the distance from the sacral hiatus (properly situated, itself) to the tip of the dural sac, averages 46-50 mm. ( $1\frac{3}{4}$  to 2 inches). But these averages may be very misleading, for again, 40 per cent. show a distance of less than 45 mm. This has an obvious bearing on technique, for if a needle is inserted further than 2 inches, although the sac is tapered and there is room for a needle beside it, uncontrolled movements by the patient may lead to inadvertent puncture of the low-lying sac, by the needle or ureteric catheter.

The sacral hiatus lies at the lower end of the posterior wall of the sacrum and is formed by lack of fusion of the laminae of the fifth

sacral vertebra. Two small stumps, the sacral cornua, are all that remain, and these are joined to the spinous process of the fourth, by bony arches, thereby forming an inverted V-shaped ridge, or hiatus. It is covered by a fibrous membrane through which pass the fifth sacral, and coccygeal nerves and the filum terminale: this in turn is covered by subcutaneous fat and the skin of the upper end of the natal cleft, though this surface mark is of little practical moment if the bony landmarks cannot be outlined.

Anomalous formations of the hiatus and related structures, variously estimated at about 10-15 per cent.<sup>3</sup> occur as deficiencies of the posterior wall higher than the fifth vertebra, and even all the way to the first; as variations in depth of the canal; and as bony obstructions to its entrance. The latter may make entry by a needle impossible, but bony deficiencies may still allow of successful results, provided the needle does not come out of the canal at a higher level, through the fibrous membrane covering the deficiency. Another important anomaly may be anterior and posterior foraminæ so greatly enlarged that too rapid escape of injected fluid takes place and a satisfactory height of analgesia is difficult to attain.

The introduction of local analgesic drugs into the extra-dural space through the sacral hiatus, allows the fluid to seep upwards, to the foramen magnum if desired, though the level reached is mainly dependent on the quantity injected and the speed and force of the injection.

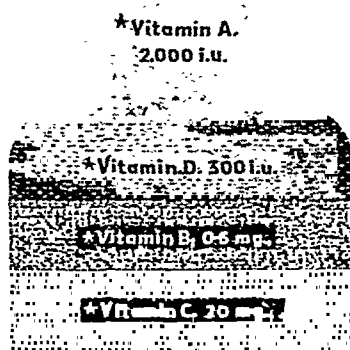
In 1933, by means of single paravertebral sympathetic block, Cleland<sup>6</sup> mapped the path of painful stimuli from the uterus, and showed that they reached the cord at the level of the eleventh and twelfth thoracic segments. This level is our primary objective. Sicard and Cathelin<sup>4</sup> have shown that fluids injected extra-durally do not penetrate the meninges, and Grodinsky and Best,<sup>7</sup> that the sub-arachnoid space extends laterally with the dura, to the dorsal root ganglia. Thus we see that not only must we inject enough fluid to reach a given height, but also enough to seep out through the foraminæ and act on the unprotected nerve sheath beyond the point of fusion of the dura. Thirty c.c. of fluid is an average amount necessary to achieve this, but the variable factors of cubic capacity of the space, density of the fatty connective tissue, size of the foraminæ and the size of the patient, are very influential, and with 30 c.c. a level of analgesia anywhere from the pubes to the xiphoid may result.

#### EFFECTS OF EXTRA-DURAL BLOCK IN, AND ON, LABOUR

During the first ten minutes of a successful injection, in labour, sacral and perineal analgesia develops, with warmth of the soles from vaso-constrictor paralysis, followed quickly by relief of labour pain which may be complete between ten and twenty minutes. Skin analgesia is not fully developed for twenty to thirty minutes, touch and pressure follow, and motor power in the legs is affected last and

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Fig. 1



Fig. 3

## Varicose Ulcer with Eczema

### *Healed beneath Pressure Bandaging*

**CASE HISTORY.** M. R. aged 40. Housewife. Varicose ulcer with severe eczema right leg. (Fig. 1)

**TREATMENT.** August 9th, 1946.—Ulcer and surrounding skin cleaned with cod liver oil. Strips of Jelonet were applied to cover the ulcer and the eczematous area, with a pad of cotton-wool over the ulcer only. The whole leg was bandaged with Ichthopaste and then with Elastocrepe. (Fig. 2)

August 23rd, 1946.—Ichthopaste and Elastocrepe bandaging repeated.

September 13th, 1946.—The œdema was reduced and the leg much less painful. Calamine lotion was applied over the whole area with a pad of cotton-wool and felt over the ulcer, and the leg again bandaged with Elastocrepe.

October 4th, 1946.—Calamine lotion, pad of cotton-wool and Elastocrepe repeated.

October 11th, 1946.—Repeated.

November 1st 1946.—Condition healed (Fig. 3). The patient was instructed to continue application herself of calamine lotion and Elastocrepe.

**COMMENT.** In this case the eczema was more troublesome than the ulcer. Both responded to the soothing effect of Ichthopaste and the firm pressure of Elastocrepe. Details and illustrations above are of an actual case. T. J. Smith & Nephew Ltd., Manufacturers of Jelonet, Ichthopaste and Elastocrepe are privileged to publish this instance, typical of many, in which their products have been used with success, in the belief that such authentic records will be of general interest.



Fig. 2

## BENE DORMIT QUI NON SENTIT QUAM MALE DORMIAT (PUBLILIUS SYRUS)

He sleeps well who does not know he slept badly.

Although they would not be classed as insomnia cases, nevertheless many patients complain that they are unable to get a good night's rest. Often the underlying cause of their restlessness is difficulty in breathing due to catarrh and nasal congestion. In these conditions free breathing may be obtained by the administration of 2 or 3 drops of Endrine Nasal Compound before retiring. 'Endrine' contains ephedrine, which shrinks the engorged mucosa, together with essential oils which soothe the inflamed membranes.



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very incompletely. The motor, or true autonomic, innervation of the uterus, appears to leave the cord over a fairly extensive number of segments above T 11, a lucky dissociation which helps us to pick off the sensory impulses and leave the motor—to the fundus: motor impulses to the cervix, thought to reach their goal via the sacral nerves, are, of course, blocked, and cervical relaxation is claimed.

Sometimes, however, as already mentioned, our preliminary 30 c.c. injection goes higher than T 11 and this may lead to a noticeable change in the contractions. Less frequent but stronger contractions may be noticed when the level is just above the umbilicus and with levels in the region of the first five thoracic segments the contractions may become ineffectual: stoppage of labour, in prematurity, by a high caudal has been recorded, but on the other hand analgesia to the clavicles has failed to prevent progress.<sup>5</sup> I have twice seen analgesia to a level of T 4 with undoubted diminution of contractions but no sign of cessation at any time; one of these patients had considerable bowel distension which was vigorously relieved over a period of an hour. Finally, mention must be made of the anal, perineal, cervical and pelvic floor relaxation which is beneficial, and the loss of bladder sensation which may be a drawback. The ability to bear down remains surprisingly good even in primigravidæ with analgesia half way up the upper rectus.

Labour is affected directly and indirectly. In the majority of cases with proper timing, first stage contractions may be indirectly accelerated by the removal of pain and fear, as by other means, and the first stage thereby shortened. In the second stage, there is no delay until such time as the untreated mother would begin spontaneously to bear down. From then on, there is no doubt of the delay unless energetic instruction and exhortation in the art of bearing down, is efficiently carried out—an efficiency which depends naturally on the enthusiasm of the exhorter and the time at his disposal.

The effect on the mother really has to be seen, for the relief of pain by means which allow *realisation* of the relief, can raise a mother with pain-driven despair bordering on hysteria, to a normal human being with, if not seen before, quite unexpected powers of co-operation and even intelligence. There is too, the inescapable psychological effect of companionship, and I have observed several cases not 100 per cent. successful by my standards, yet perfectly satisfactory to the mother, because after an hour or so we had got to know each other and she did not feel left alone to get on with it. In a few words, a mother under caudal analgesia is content, even happy, unalarmed, able to eat and drink, unfatigued mentally and bodily and very willing to listen to an outline of what she must finally do before her baby is born.

About the effect on the foetus there is no controversy. It is immeasurably better off than when born under the influence of centrally acting drugs, though there are points to note in the technique which chiefly concern the foetus.

I began the method on cases of perineal tears and once I felt I was acquainted with the female sacrum, I tried single injections of procaine in labour. I was very pleased with its effect and went on to try Hingson and Edward's continuous technique of repeated injections through an indwelling needle. I also tried injection through a ureteric catheter, and the continuous drip method with the needle. In those days the needle was not malleable and I had to keep the patient on her side the whole time. Against the ureteric catheter was the size of needle needed to introduce it, as at present available in this country. Nor was I lucky with my attempts with a drip mechanism, though that was probably my own fault. Each of these methods, however, was so enormously time consuming, needing, as they did, constant attention and attendance on my own part, that I soon reached the conclusion that we had neither the medical nor nursing-staff power to cope with an attempt to imitate our American colleagues. In fact I believed then, as I do now, that if the method were to be of any use in this country it would have to be by injection of a drug lasting a great deal longer than procaine, given in one injection and the needle removed. Amethocaine alone has not been successful with me.

In 1947 Dr Frank Holmes of the anæsthetic department at the Royal Infirmary, joined me in another attack on the problem and as he had considerable experience of the method in general surgery I learnt a great deal. I hope he learnt a little about normal labour at the same time. The difficulties of two of us, however, being free to carry out prolonged attempts, at the same time as there was a patient in labour at the proper stage, curtailed our joint work to no more than 25 cases, including some for operative delivery. During that time we achieved an original malleable needle from America, and broke it on its second time of use. I also broke a nylon catheter in 1948. Nevertheless, the effective cases were so gratifying that last year I started to use the technique described by Willis E. Brown<sup>8</sup> following a procaine injection to ascertain the amount of drug necessary, by an injection of amethocaine (also known as pontocaine and decicain) and removal of the needle. This, I have found, may last anything from three to five and a half hours, and half an hour after the needle is out, the full effect of the drug has taken place and the patient may be left and another patient treated. Had we trained staff to leave with each patient, even more could be undertaken at one and the same time. Before I describe the technique, I should like to emphasise what is the outstanding danger, and that is the introduction of a massive dose of analgesic drug into the spinal theca. Towards avoidance of this disaster many of the details of technique are directed. To be sure, other complications can arise but they are comparatively insignificant and comparatively easily surmounted.

To begin with then, oxygen must be readily available. For position I prefer the left lateral with the right knee drawn well up, to give the optimum exposure of the region. Next, the area is properly cleansed

first with soap and water and finally several applications of iodine. I usually put an occluding swab over the anus itself before draping the patient. Then the hiatus is found by placing the tip of the left middle finger on the coccyx and feeling for the hiatus with the side of the thumb: once found, the index finger is placed on it and a skin weal is raised. The caudal needle is then inserted at an angle of about  $45^\circ$  with the skin, through the membrane covering the hiatus, till it touches the anterior wall of the sacral canal. As most of the vessels in the canal are anterior, the needle should then be withdrawn a fraction, swung till it is almost flush with the skin and pushed up into the canal. If it hits the posterior wall, a little pressure against the hiatus will ensure that it is freed, to enable it to be inserted yet higher though there is nothing to be gained by putting it higher than  $1\frac{1}{2}$ -2 inches. A 19-gauge needle  $2\frac{1}{2}$ -3 inches long is quite adequate. Once inserted the needle should be watched for escape of cerebro-spinal fluid; secondly, gentle aspiration should be carried out with the same point in view: forceful aspiration may suck the dura against the bevel of the needle and obscure the test. To find out if the needle has been placed posteriorly to the sacrum a few cubic centimetres of air may then be injected,<sup>9</sup> while if it is thought that the needle has gone anterior to the sacrum (a much rarer occurrence), a rectal examination will clear up the point.

If cerebro-spinal fluid appears the method should be abandoned for that patient. If blood appears the needle should be moved and ten minutes allowed for thrombosis, otherwise intravenous injection of procaine may occur. I have never seen cerebro-spinal fluid, but blood quite often, and twice I have seen procaine excitement and confusion, the second time including a convulsion which lasted ten seconds.

A test injection of 6 c.c. of 2 per cent. procaine may now be given, the third, and this time a functional, test to avoid massive spinal injection. If, after a full ten minutes there is no sign of spinal effect—relief of pain and loss of power in legs—then the full 30 c.c. dose may be injected. If the needle is correctly placed the injection is easy and should be made rapidly but not forcibly. If it is not easy, the needle should be withdrawn slightly as it may be in the canal but under periosteum. If the needle is posterior to the sacrum a procaine tumour is raised which may be felt for and discovered before it is big enough to be visible.

If in ten minutes, the effect is obviously not enough, as judged by pricking of the skin as well as observing pain relief, then more procaine is added until pain is relieved. If more fluid is injected sooner, too high an effect may be produced and if much later the level may not be raised at all. When the full effect of the procaine has been achieved, then amethocaine 1:1000 with adrenalin 1:200,000 is injected, to prolong the analgesia, the needle removed and the patient turned on to her back. The amount of amethocaine to add can only be judged by practice and 25-30 mgms. diluted in 30 c.c. (or more, if more



procaine was necessary) is probably the upper limit of safe dosage, for toxic reactions from amethocaine begin to occur with doses of 35-40 mgms. and over (Brown, *loc. cit.*). Even with satisfactory results from the procaine, however, the time that the amethocaine lasts is both variable and unpredictable, and the ideal agent has yet to appear. Xylocain, now being used in Stockholm, seems a possible improvement.<sup>10</sup>

The remainder of the technique takes the form of observation of blood pressure, bladder fullness, and progress of labour. With analgesia to the umbilicus there is little drop in pressure though a temporary fall may follow too rapid an injection. At higher levels, with slow injection, there is still remarkably little drop compared with higher spinal anæsthesia, but again speedier injection may reduce the pressure to levels dangerous to the foetus and pressure readings with auscultation of foetal heart sounds should be carried out until the full effect of the last dose can be judged to have occurred. Methedrine should be available to correct too great a fall in pressure.

The most helpful description of the method I can recommend, is to be found in Pitkin's *Conduction Anæsthesia*. Also Peel and Galley<sup>11</sup> in this country, should be read, and especially their letter<sup>12</sup> answering a renowned but disapproving obstetrician, caught out in armchair criticism.

#### DISCUSSION AND ASSESSMENT

Hingson's most recent summing up,<sup>13,14</sup> after collating some 200 papers representing some 600,000 patients so treated, comes to very modest and important conclusions and I can as yet set no numbers into a series, for analysis and scrutiny as a series.

In the 78 cases of which I have experience, 11 were for operative work solely and 67 for relief of labour pains. Of these 67, 5 were complete failures and 6 only achieved a saddle analgesia. Out of the remaining 56 the methods and timings were so varied as to preclude any forming of tables and percentages. Dr Holmes and I satisfied ourselves of our ability to carry out a continuous technique, but we had not the time and we drifted apart—or rather failed to drift together often enough. With the procaine and amethocaine method I can speak of 17 cases with an average duration of analgesia of four hours. No mothers have died or suffered any after effects and the only foetal loss I have had was a premature infant (thirty weeks) which only lived twenty-four hours.

I can therefore only outline my own conclusions on the value of a manœuvre which sets the labouring mother free of pain for four to five hours, and discuss at what stage in labour it may be best used.

Now that the hue and cry of the *Reader's Digest* and other lay press irresponsibilities has died down it is possible to view the situation more calmly—though there is at the moment, we should not forget, a hue and cry for more planning towards relief of labour pains, in this country.

Hingson insists :—

- (1) That caudal analgesia is a hospital procedure necessitating the full panoply of asepsis, antisepsis, and the anæsthetist's trolley for dealing with complications, readily available.
- (2) That the method is *not* for the relief of the discomforts of early labour which can well be taken care of by other means.
- (3) That labour should be established, the head engaged, the primigravid cervix 5-6 cms., and the multiparous 2-3 cms., dilated and taken up, the pains lasting thirty seconds at least and occurring every three to four minutes.

It will be seen that these criteria, which I heartily endorse, narrow the scope of the method considerably, and even in U.S.A., where many more mothers have their babies in hospital than here, the proportion receiving caudal analgesia is still small, though 1000 clinics are regularly using it. Hingson still uses the malleable needle, and keeps the patient in the left lateral position until sufficient replenishing doses of metycaïne (roughly every three-quarters of an hour) have brought her to the point of delivery when outlet forceps are applied if spontaneous delivery is not soon forthcoming. He states that the effect of repeated doses gets less after about eight hours and that the average duration is five to six hours. This is very little more than can be achieved by Brown's procaine and amethocaine technique and raises the questions for us in this country, just when do we prefer to begin the relief of labour pains, and how long do we wish to continue it? I think that most of us would agree that the early discomforts are most commonly dealt with nowadays by chloral or some barbiturate, the next and more painful period by pethidine or morphine, taking the patient through the approach to and into, the second stage, and finally for the second stage and delivery some inhalational method such as gas and air or trilene. Substitute caudal analgesia for the pethidine or morphine, and the time of benefit is much the same, but we may be given a new problem by taking away the spontaneous desire to bear down, and we are again faced with the question of outlet, or prophylactic forceps, which twilight sleep so often entailed—with the difference that with caudal analgesia, the foetus is far from sleepy: and this is a very big difference.

Occasionally the analgesia, by lucky timing, wears off about an hour before delivery and the mother, being *consciously refreshed*, is in an entirely different state of mind for tackling the job in hand. More often, when this timing is attempted, analgesia wears off first at the upper level so that pains return before vaginal sensation, and again the question of low forceps arises. I now recognise three different timings of caudal analgesia. That mentioned above where it wears off before delivery. That in which outlet forceps are applied during the caudal analgesia if spontaneous delivery does not appear probable (an increase in the forceps rate in primigravida chiefly, as Galley and Peel emphasised, and which must of necessity be almost wholly laid

at the door of the analgesia). And that in which a single injection of procaine is given for delivery only, after the patient has spontaneously begun to bear down. All three methods are appreciated by the mother, to a degree not possible in one drugged by the "drowsy syrups," or struggling with a gas and air machine and I must confess to a great deal of inner satisfaction in changing the facial expression of a tormented mother to one of happy, cheerful interest. But I am no purist in this matter and have no hesitation in covering any remaining discomfort arising from unsatisfactory analgesia, by gas and air or trilene, in exactly the same way as for pudendal nerve block. I like it, the mother likes it, the foetus likes it, even Greenhill<sup>15</sup> likes it, saying that there is no more satisfactory and pleasant type of analgesia "when performed properly without mishap." But he lays down very sensible rules for how it should be done, only acknowledging for it a "limited field of usefulness."

A brief word about indications and contra-indications. The indication which one would like to attend to is simply any uncomplicated labour: but the process is too time-consuming ever to reach that pitch without an entirely different organisation of analgesia for labour. The medical indications are those for which many already prefer local anæsthesia—affections of the lungs, of the heart, diabetes and pre-eclampsia, and, par excellence, *prematurity*. The contra-indications are equally simple to list. Short of obesity, sacral anomalies, or skin sepsis making the method impossible (not true contra-indications) the obstetric contra-indications are chiefly disproportion and antepartum hæmorrhage and it may be used in the latter preliminary to abdominal section after examination. Known foetal monsters are sometimes looked on as a contra-indication, but this is a matter of personal choice and confidence, as is use of the method in hysterical patients. There is no evidence that central nervous system disease is aggravated but it is usually looked on as a contra-indication. *Tapping of the spinal theca is an absolute contra-indication.*

In occipito-posterior cases there may be less resistance to stimulate the long rotation if that factor is regarded as significant. I have not had any cases with delay attributable to this position but several with transverse arrest (easily delivered under caudal, after rotation) which may, of course, have been posterior initially. I have not tried any breech deliveries, but if I did I should prefer a low caudal to ensure, rather than hope for, efficient bearing down efforts: but that is purely personal preference, for I like breech cases to be conscious and hard at work, unless a breech extraction is needed. In the matter of results, Hingson claims better figures in almost every aspect (blood loss, morbidity, subinvolution and maternal mortality, and foetal loss of all types—this latter point being the entire subject of his most recent paper) but of course with choice of only straightforward labours, many "sticky problems" are thrown into the scale against the controls.

Without wishing to raise serious discussion on a controversial point,

but to air a problem which is coming whether we wish it or not, I must just ask you to consider who should carry out any analgesia in labour? And remembering that by the method I have outlined, and most others, it is a necessary preliminary to forecast the time of delivery (as opposed to the continuous caudal) I see no escape from the decision that the operator must be thoroughly trained in obstetrics, and I would advise him to make his own mind up about the distance in labour at which his prospective patient has arrived. The report of the American "Committee on the Study of Continuous Caudal Anæsthesia" is very downright on this point and it concludes "Until such a time as its safety can be determined, we must say that caudal anæsthesia has a limited place in obstetrics, and should be limited to the obstetrician trained to administer the drugs, and who has time for its supervision."<sup>16</sup>

That last point—time—is its chief drawback for us in this country, and will remain so for many years to come, as far as labour is concerned; and had it not been for the kindness of the staff at the Simpson Memorial Maternity Pavilion, Dr Miller, Dr Fahmy and Professor Kellar, and of Dr Morris at the Western General Hospital, I should not have gained even this very small experience. I wish to offer them my sincere thanks, and also Dr John Gillies for much help and advice.

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#### DISCUSSION

*Dr Richard de Soldenhoff* said his own experience of caudal analgesia was limited to 10 cases in which he had himself taken charge of the administration. He had found the method effective but too exacting in its demands upon his time to make him anxious to continue its use. He added his support to Dr Anderson's recommendation that only those well versed in obstetrics should

undertake to administer caudal analgesia, owing to the impossibility of timing the injection without much experience of normal midwifery.

*Dr D. S. Middleton* said he had no personal experience of this method in obstetrics, but that he had used it for minor surgical procedures, chiefly in urology. He stressed the importance of always keeping a stilette in the lumen during the insertion of the needle if breakages *in situ* were to be avoided.

*Dr John Gillies* said he felt there was much to be said in favour of caudal analgesia provided the person administering the drugs took his duties seriously and gave his whole attention to the observation of his patient. Danger was likely if the method were employed as a slipshod piece of mere surgical routine, as had at one time been the case with spinal analgesia. He agreed that the method of continuous administration had many disadvantages. It was a matter of regret that as yet no local analgesia of really adequate duration of action had been devised, although the preliminary reports on "xylocain" were encouraging and led him to support the view that a reliable period of five hours' relief from pain might shortly be found possible.

*The President* said he felt that there was now a definite field for the application of this method, despite the fact that general experience in hospital and private practice convinced him that other methods of simpler nature were usually adequate for relief of pain in normal cases at term. It was in the interests of the premature infant that caudal analgesia appeared to him so particularly useful. Most obstetricians of experience had noted how frequently premature labours were distressful and prolonged, with the mother suffering so considerably as to call for some measure of relief. It was in just such cases that the exhibition of the mildest sedatives might be followed by the birth of a seriously narcotised baby, the resuscitation of which might be difficult. These difficulties could be overcome by judicious caudal analgesia, and to him the single dose technique was more attractive than the continuous or multiple dose method. On a recent visit to America he had found a general reluctance amongst senior obstetricians to apply continuous caudal analgesia, which many had described as too dangerous. He thanked Dr Anderson for reading to the Society its first paper on this subject.

*Dr Anderson* replied.

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## ANÆSTHESIA FOR CÆSAREAN SECTION

By J. D. BOURKE, M.B., B.Ch., B.A.O. (N.U.I.), D.A. (Eng.)

*Department of Anæsthetics, Royal Infirmary, Edinburgh*

OPINIONS of obstetricians and anæsthetists as to the best anæsthetic technique for cæsarean section differ widely, especially with respect to the employment of spinal block for that particular operation. Whatever method is chosen must not cause fœtal depression or danger to the mother; diminished contractility of the uterus and so predispose to post-partum hæmorrhage; induce psychic trauma; or delay unduly the post-operative recovery of the mother. The anæsthetic techniques available are:—

- (1) General anæsthesia.
- (2) Local analgesia, including spinal.

Certain problems peculiar to advanced pregnancy arise in relation to the choice of management of the anæsthetic in cases of operative delivery.

### PROBLEMS

*Individual Pathology.*—The type of patient and any pathology she exhibits must be assessed. Important in this category are the toxæmias of pregnancy, eclampsia and accidental hæmorrhage, factors which may readily be aggravated by an ill-chosen or badly managed anæsthetic technique. Of significance also are various concurrent conditions such as diabetes, tuberculosis and occasionally thyrotoxicosis, and appropriate allowance must be made for associated disturbances of metabolism and endocrinal balance. The latter accompanies pregnancy fairly frequently and it is interesting to note that Seyle (1943) showed that the action of anæsthetics is potentiated by the sterols progesterone and desoxycorticosterone. Modifications of anæsthetic technique in respect to the altered activity of the endocrines of the pregnant woman need further study.

*Premedication.*—This is not essential, but atropine 1/100 gr. intravenously before general anæsthesia prevents excessive secretions of mucus and consequent interference with gaseous exchange in the alveoli. Morphine should not be given before the delivery of the infant except possibly when local analgesia is employed. For thyrotoxic cases hyoscine 1/100 gr. is preferable to atropine which is a metabolic stimulant.

Because of the minimal nature of the premedication the patient is conscious of what is going on around her. Some are very nervous and it is important that the anæsthetist does nothing to increase this thereby causing a difficult induction. Thiopentone is a simple solution of the difficulty but its use may cause fœtal depression.

Paper read at the Obstetrical Society of Edinburgh, 12th January 1949.



*Full Stomach.*—Vomiting often occurs in the pregnant woman especially if the operation is performed at short notice. Aspiration of the gastric contents prevents this. The tube may be left *in situ* during the operation to promote drainage.

*Laryngeal Spasm.*—Hypoxia from laryngeal or other causes will depress the foetus and must be avoided at all costs. Variation in the foetal heart rate may be used as evidence of such hypoxia. Intubation may be necessary to restore the airway.

The adoption of a steep Trendelenburg position in the pregnant woman during the maintenance of the anæsthetic throws a severe strain on the peripheral respiratory mechanism. The use of drugs which produce unconsciousness and medullary depression abolish compensatory reflex mechanisms and efficient breathing may become impossible. Furthermore the regurgitation of gastric contents is common in such a position.

In short, the factors to be considered are :—

- (1) The type of patient and her individual pathology.
- (2) The absence of adequate premedication involving a difficult induction during which incidents such as vomiting, laryngeal spasm, etc., are likely to occur, and finally, probably the most important and least recognised—the strain thrown upon the respiratory mechanism due to the Trendelenburg position and the abdominal tumour.

With these facts in mind let us consider the techniques available.

### SPINAL ANALGESIA

There is no more controversial subject in the whole field of anæsthesia than the question of spinal analgesia for cæsarean section. Those in favour of this technique quote large series of cases without mishap to mother and infant, and dogmatically assert that it is the method of choice. The opponents of the method quote the occasional death which occurs and rightly stress that such an occurrence is indeed a tragedy. Furthermore they point out that the deaths which have occurred have never been adequately explained. On these grounds they condemn the use of spinal analgesia.

The effects of spinal analgesia are :—

- (1) Motor—Varying degrees of muscular paralysis.
- (2) Sensory—Sensory loss.
- (3) Vasomotor—Arteriolar dilatation—fall in B.P.
- (4) Visceral—In this particular case—hypertonus of the uterus.

The degree and extent of these effects depend upon the number of spinal segments paralysed.

For cæsarean section the optimal level of the spinal anæsthetic is T 5-6. This may appear unnecessarily high, but recent work has shown that sensation may be transmitted via afferent visceral fibres of

the sympathetic, and for complete analgesia these fibres up to T 5 must be blocked for any intraperitoneal manipulation.

A spinal block to the level of T 5 has three disadvantages.

(a) It causes paralysis of the lower five intercostal muscles and also the accessory abdominal respiratory muscles. This interference in normal subjects (without abdominal tumour) is compensated for by increased diaphragmatic movement and an adequate tidal exchange may be maintained, even in the presence of gross pulmonary disease. In the pregnant parturient woman, however, this compensation is incomplete and the additional strain of a steep Trendelenburg position by encroaching on the volume of the thoracic cage further reduces tidal exchange and anoxia will inevitably result. The degree of anoxia will determine the fate of the mother and infant.

(b) It causes paralysis of the vasoconstrictor fibres controlling arteriolar tone with a resultant fall in B.P. In normal individuals this fall may not exceed 15 per cent. and is of no real significance. In the pregnant woman, with a greatly increased vascular capacity in the lower abdomen, it may be anticipated that a greater fall in pressure may occur. This, combined with the anoxia due to the lowered vital capacity, may precipitate rapid circulatory failure and even death.

(c) The third disadvantage which one must consider in such an operation as cæsarean section is that of loss of blood. Burch and Harrison (1930) have clearly demonstrated that patients under spinal analgesia do not tolerate hæmorrhage, particularly rapid loss of blood, largely because the compensatory mechanism for reduced blood volume is paralysed.

In short we may say that (a) interference with the respiratory apparatus, (b) partial vasomotor failure and (c) the serious effects of a small rapid hæmorrhage are valid objections to spinal analgesia.

In the face of these facts it would appear that spinal analgesia as such should not be the method of choice for cæsarean section, particularly if the anæsthetist has a limited experience with this technique. Moreover it should never be used in cases that come to operation with a low blood volume, *i.e.* cases of accidental hæmorrhage and placenta prævia. I am sure that if a careful analysis were made of these so called inadequately explained deaths under spinal analgesia it would be found that a large number of the cases would belong to these categories.

In certain types of cases, *i.e.* the toxæmias of pregnancy, diabetes, thyrotoxicosis, etc., where the extensive metabolic derangement is the main issue the administration of spinal analgesia must be seriously considered.

- (1) It effects analgesia to an extent and degree out of all proportion to the amount of toxic drug used and does not directly interfere with cell metabolism.
- (2) It presents the surgeon with operative conditions which facilitate rapid surgery.
- (3) The denervation of the uterus causes increased tonus and less loss of blood.

It would be fair at this point to state that two of the main disadvantages already stressed, namely respiratory and vasomotor failure, can be greatly reduced by a technique of light general narcosis combined with spinal analgesia. By means of this technique responsibility for respiratory function (adequate) can be taken over by the anæsthetist and blood pressure and circulatory function can be maintained by pressor drugs or blood transfusion. To maintain light general narcosis, minimal dosage only, of cyclopropane or thiopentone should be used and adequate oxygenation assured. Under these conditions the use of spinal analgesia for cæsarean section is a justifiable procedure.

### GENERAL ANÆSTHESIA

Lanahan and Taylor (1943) in a three-year survey of anæsthesia for obstetric operations have shown that general anæsthesia is the most commonly used technique and ether the most popular agent. In the Simpson Memorial Maternity Pavilion general anæsthesia has been the anæsthetic of choice and the results have been satisfactory. The disadvantages, in short, are :—

- (1) Toxic drug (ether or chloroform) may be used and these are likely to produce foetal depression.
- (2) General anæsthesia, particularly with chloroform and ether, depresses the contractility of the uterus and may precipitate post-partum hæmorrhage.

If these disadvantages are realised, general anæsthesia can be made safe for mother and infant by (a) reducing the time between induction and delivery to a minimum, (b) avoiding suboxygenation, and (c) maintaining as light a plane of anæsthesia as possible until the infant is delivered.

Cyclopropane, the agent of choice in the Simpson Memorial Maternity Pavilion, overcomes the disadvantages of toxicity and depressed contractility of the uterus.

### CURARE

The introduction of curare into obstetric anæsthesia has been of great service in that good relaxation can now be obtained and some harmful reflexes obtunded without recourse to deep and toxic levels of anæsthesia. By producing favourable operating conditions the time between induction and delivery has been reduced. It would appear from the meagre experimental evidence available that curare does not cross the placental barrier and affect the foetus. In the Simpson Memorial Maternity Pavilion our results with curare have been good. The majority of infants delivered have breathed within one minute and the longest time taken for complete resuscitation has been eight minutes. It must be realised, however, that curare itself will interfere with maternal respiration and should not be lightly used. The dosage should be minimal and in this unit 10 mgms. of *α*-tubocurarine chloride has been found satisfactory.

## LOCAL ANALGESIA

While local, regional and caudal methods are time-consuming they are occasionally ineffective and the patient is subjected to a barrage of stimuli affecting her psychic centres and general anæsthesia has to be resorted to except in the completely stoic type. Of course when successful there is no effect on the foetus. They should be used when there is gross foetal distress and when contra-indications for spinal analgesia and general anæsthesia exist. Local wall block should not be used in the obese patient because of the amount of drug needed and the danger of areolar tissue sloughing. Procaine and amethocaine, because they contain *p*-amino-benzoic acid group, will inhibit the action of the sulphonamides. It is claimed that local analgesia delays the healing of the wound.

Anæsthesia, for cæsarean section, must have as little effect as possible on the mother and infant. In the light of present knowledge each case must be considered on its merits before the anæsthetic is chosen. Further, it is well to remember it is more essential in this type of antæsthesia to realise the choosing of anæsthetist is more important than choice of anæsthetic.

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## DISCUSSION

*Dr W. F. T. Haultain* said he personally would like to thank Dr Bourke not only for his paper but for the number of excellent anæsthetics he had administered for him for cæsarean sections for many of which anæsthesia was difficult and fraught with danger. He had not personally encountered serious danger from gastric regurgitation during general anæsthesia, but thought Dr Bourke's warning on the subject was timely. He had observed, for example, that in the 1947 report of the Royal Victoria Infirmary, Montreal, two maternal deaths had occurred from this cause. He did not agree that morphia was ever indicated in premedication for cæsarean section, even when local analgesia was contemplated. The effects upon the child might be disastrous. He himself used a combination of pethidine and hyoscine, without serious difficulty. He considered that Dr Bourke's experience with curare was particularly fortunate in that all babies cried within eight minutes. Dr Haultain considered that such liveliness did by no means always occur with cæsarean sections on patients who did not receive this drug. He said the introduction of cyclopropane had made cæsarean section a much less formidable procedure. His collection of the frequent heavy blood loss which occurred with the old chloroform-ether sequence convinced him of this. However, he wished to emphasise and was sorry Dr Bourke had not emphasised the need to avoid the injection of posterior pituitary extract to the patient anæsthetised with

cyclopropane. There was a very real danger of maternal death in such circumstances, and it was therefore always advisable to employ ergometrine if an oxytocic were required.

*Dr Richard de Soldenhoff* said his own experience had been gained initially in districts where good anaesthetists were scarce and in such circumstances he had become enthusiastic for the use of local infiltration analgesia, supplemented by the intravenous injection of pentothal immediately prior to the incision of the uterus to avoid the discomfort not infrequently amounting to pain which the patient experienced as the head was brought through the lower segment incision and 36.5 per cent. of the 80 caesarean sections done in 1948 were by this method. He had no fear that the baby might be affected by pentothal given at that time. He had records of a number of cases in which he had had the cord blood examined for pentothal, but never had the analyst been able to detect even the minutest trace. His recent experience with general anaesthesia had been entirely satisfactory. His anaesthetist, Dr David Armstrong of Ayr, had given cyclopropane with curare for 40 per cent. of those done in 1948. The technique was to give 8-10 mgms. of tubo-curarine immediately before commencing the cyclopropane administration, a subsequent dose of 5 mgms. being given just prior to the closure of the abdomen. His personal experience with spinal analgesia had been with heavy "nupercaine" of which he was accustomed to give a maximum of 1.6 ml. He had found a very serious fall of blood pressure with the larger dosage of 2-3 ml. recommended by Rufus Thomas.

*Dr Suzanne Paterson* said her preference was for spinal analgesia with heavy "nupercaine" in dosage of 1.75 ml. preceded by ephedrine 50 mgms. given half an hour before. Intravenous pentothal was given just before opening the abdomen. She found that the babies cried very promptly and was surprised that Dr Haultain should consider that a baby might frequently go as long as eight minutes without doing so.

*Dr Caroline Elliot* said her preference was strongly for local anaesthesia. The effectiveness of this was much increased by consideration of the patient's feelings by maintenance of silence in the operating theatre, with no speech other than essential instructions. This must be impressed on the whole staff. She was accustomed to use pre-medication with omnopon and hyoscine, and had not noted any adverse effects on the foetus, as seemed a danger if used prior to general anaesthesia. She combined local with pentothal, delaying administration of the latter until immediately before uterine incision. She had the impression that slight wound infection was possibly a little more common after use of local infiltration, especially in obese patients.

*Dr Alison Ritchie* said that she had been convinced that local analgesia was extremely safe for mother and for child, but doubted whether this increased safety was enough to justify the pain which the patients suffered during the extraction of the child. She felt that general anaesthesia with cyclopropane was preferable. She agreed with Dr Haultain that the old-fashioned chloroform-ether sequence was apt to be associated with atonic uterine haemorrhage. She knew of two such cases which ended fatally. This difficulty could be avoided with the new techniques. In the induction of anaesthesia, she was uncertain of the place of pentothal which was liable to cause spasm and vomiting. If it were to be given, she advised not more than 3 ml. of

5 per cent. pentothal solution, to be given very rapidly and followed at once by cyclopropane. For spinal analgesia, she preferred procaine to "nupercaine." In her experience there were fewer disagreeable sequelæ with the former drug. With spinal analgesia she recommended a supplement of light general narcosis. She made a special plea for care in the diet of patients in labour. The frequency of vomiting during the induction of general anæsthesia was often associated with the unwise forcing upon the patient of large quantities of solids or fluids. She recommended restriction of intake of food and drink for all patients likely to require an anæsthetic.

*Dr F. G. Gibbs* said he wished to support Dr Ritchie's plea for careful feeding of the parturient. His own personal experience of anæsthesia for cæsarean section dated from the time when he was anæsthetist to the late Dr F. W. N. Haultain. In those days chloroform or ether or various mixtures were employed and he did not recollect that the patients did badly. He felt the anæsthetist should not be subject to any strict routine method of anæsthesia, but should be free to use whatever drug or technique he considered desirable for the individual patient.

*The President* said he favoured local anæsthesia coupled, if necessary, with pentothal, though local analgesia was unsuitable in some cases. In a classical cæsarean section the addition of pentothal was seldom necessary, but in the lower segment operation its use was of great value just before the uterus was incised. If the baby was delivered within seven or eight minutes of the injection of pentothal, no untoward results occurred. Cæsarean section under general anæsthetic yielded a child whose full respiration was much delayed as a rule in comparison with that of a child delivered spontaneously through the natural passages. Cyclopropane was not an innocuous anæsthetic in regard to the foetus as clinical experience had proved that foetal respiration could be definitely depressed by it; and from the maternal aspect it could not be denied that cyclopropane was followed on occasion by pulmonary complications of some severity.

Spinal analgesia had a very definite place and was certainly less dangerous than it was claimed by many observers. Given skilfully and with attention to detail, results had shown that spinal analgesia carried very little risk to the mother, and the fact that it did not affect the foetus was a point very greatly in its favour, particularly when dealing with a premature infant.

## TWO CASES OF CONGENITAL ABNORMALITIES OF THE GENITAL TRACT ASSOCIATED WITH PREGNANCY

By M. J. D. NOBLE, F.R.C.S., M.R.C.O.G.

Obstetric Unit, Western General Hospital, Edinburgh

I WISH to describe to you two rather interesting cases illustrating congenital abnormalities of the genital tract associated with pregnancy which we have had in the Western General Hospital recently.

The first is a case of partial congenital atresia of the vagina associated with pregnancy. The patient, a Mrs R., paid her first visit to the ante-natal clinic on 1st November 1946 and was booked on account of bad home conditions. She was a primigravid woman, and at that time at the twelfth week of her pregnancy. Routine examination showed nothing abnormal. However she gave a history of bladder trouble for many years. As a child she was admitted to the Royal Hospital for Sick Children, Yorkhill, Glasgow, at the ages of two years, four years and six years on account of a "chill on the kidneys." However, she was unable to recall any of the symptoms. Since then she had always been troubled with what she described as a weak bladder in her early years and had been troubled at this time with a severe degree of frequency of micturition having to rise several times at night. This latter symptom had improved as she had grown older, and recently she had managed to do without getting up at night almost completely.

Her pregnancy was uneventful until the thirty-sixth week at which time a routine vaginal examination was carried out. When this was attempted, it was with great difficulty and some considerable discomfort to the patient that one finger could be introduced, and an examination of the pelvis was found to be impossible. On moving the finger round the cervix could be felt rather posteriorly and there was a layer of tissue between it and the examining finger. The foetal head could also be felt engaged in the pelvic brim and when the finger was removed a quantity of fluid came away. It was therefore decided to admit the patient to hospital at once for further examination.

The following morning a full investigation was carried out under general anaesthesia with the patient in the lithotomy position. The external genitals were swabbed down and the patient draped in the usual way. The labia majora, which were somewhat hypertrophied, were retracted and fixed to the sides of the lithotomy sheet with tissue forceps. The external genitals were now inspected. (Fig. 1 and 1a). Posteriorly no normal vaginal orifice or hymen were present. These were replaced by a small mound of tissue, to the upper and left of

Read at a Meeting of the Edinburgh Obstetrical Society on Wednesday 11th February 1948.

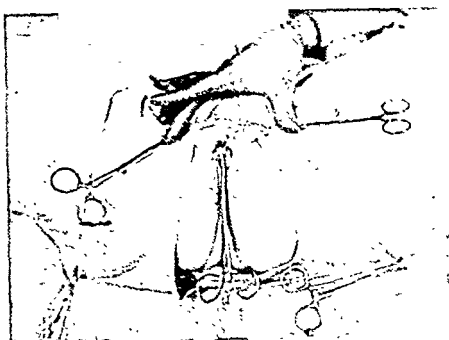


FIG. 1.

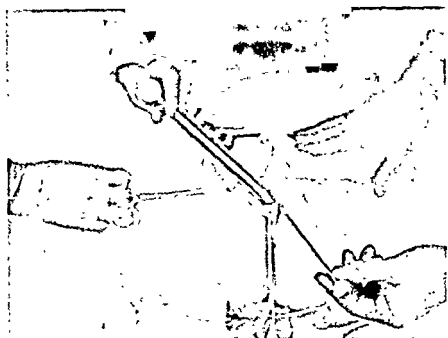


FIG. 1a.



FIG. 2.



FIG. 3.





which, there was a small opening about 5 mm. in diameter. A probe entered this for about one inch and was then arrested. Just above this mound of tissue the urethral orifice could be seen. This and the urethra behind were very much dilated, and a finger could very easily be introduced along it into the bladder, and it was along the urethra that the finger had been passed the previous day. A small band of tissue could be felt just as the finger entered the bladder, this was the grossly dilated sphincter. As the finger was removed some fluid, now recognised to be urine, came away. A cystoscope was next introduced into the bladder, and the latter distended to 300 c.c.'s with water, beyond this considerable leakage took place owing to the dilated urethra. The bladder mucosa, as seen through the cystoscope, was quite normal in spite of the fact that Dettol cream had been used for the previous examination, and the ureteric orifices were normally situated. There was a shadow present in the upper part of the bladder which was thought to be probably due to the foetal head. A sound was again passed into the small opening below the urethra and guided up by a finger in the urethra. It could be felt passing up for about an inch when progress was arrested. A search was then made for further orifices but none were found.

Before completing the operation a finger was passed into the rectum and here, rather high up on the anterior wall, a normal cervix could be felt, partially taken up and one finger dilated.

When she recovered from the anæsthetic, Mrs R. was closely questioned about intercourse with her husband. This, she said, had been extremely difficult and painful at first, but had become a little easier after the first two months. She was actually only married for six weeks before becoming pregnant. Complete satisfaction was, however, obtained by both parties.

Thus it could be seen that this patient had no vaginal orifice at all, and that during intercourse her husband had dilated her urethra. Some small orifice must have existed somewhere since the patient had become pregnant a very short time after marriage, and had also menstruated satisfactorily for nine years; but whether this was situated in the region of the urethra or on the mound of soft tissue, could not be determined at this stage. Now, since there was no vaginal orifice one could not be certain whether there was any satisfactory vagina and this introduced difficulties with regard to labour. Was one to leave the patient to go into labour spontaneously? If there was no vagina then considerable damage might be done to soft tissues by the descending head. It was therefore decided to carry out elective cæsarean section and to try to investigate the condition of the soft parts from above at the same time. At this stage it was thought that the opening might possibly be in the urethra and, although menstruation had taken place satisfactorily, one had considerable doubt about the lochial discharge.

Just before operation the patient had an intravenous pyelogram

carried out to determine if there were any abnormalities of the urinary tract and a double ureter was found on the left side.

The patient's expected date of delivery was 19th May 1947 and elective cæsarean section was carried out on 16th May 1947 under cyclopropane and oxygen anæsthesia.

The patient was swabbed down with acrimine in spirit from the costal margin to her knees. Her legs were then wrapped in sterile towels and held by sterile assistants, the lower part of the operating table having been removed, and her vulva placed at the edge to be convenient for any manipulation later on. The abdomen was draped in the usual manner. The latter was then opened by a right paramedian incision and the child delivered through the lower uterine segment. Sinuses in the lower segment were then clamped to prevent bleeding. A finger was next passed down into the lower segment and the cervical canal defined. The vaginal fornices were then defined and the vagina explored to the limit of touch without encountering any obstacle. Following this a No. 14 double ended Hegar's dilator was passed through the cervix and guided down helped by the finger of another operator in the rectum. It was found to pass down until the end encountered the mound of tissue below the urethra. A uterine sound was then passed through the small sinus to the left of the mound, and this time it passed right through and could be felt grating against the metal dilator inside. This then established the external communication with the vagina. A scalpel was next used to incise through the mound of soft tissue on to the Hegar's dilator. The latter was then pulled through from below, a part of the mound was excised, and the edges stitched with interrupted catgut sutures. Simultaneously the incisions in the lower uterine segment and the abdominal wall were closed in the usual manner. Following the excision of the tissue below the vagina was explored. It was rather small and just admitted one finger.

The tissue excised was sent for microscopical examination and reported as a piece of rather fibrous tissue covered on both sides with squamous epithelium.

The patient's puerperium was uneventful and the lochia drained normally. The urinary symptoms improved rapidly and there was no infection of the urinary tract. By the time the patient was discharged the vulvar wound had healed and one finger could be introduced into the vagina.

Since discharge the patient has improved slowly. The vagina will now admit two fingers and the urethra is considerably reduced in size. The frequency also has almost entirely disappeared and intercourse is much easier.

This, then, illustrates a case of partial congenital atresia of the vaginal introitus due probably to a failure of the end stage of the breakdown of the septum dividing the cloaca from the ends of the Müllerian ducts. The atresia was not complete as evidenced by the fact that the patient

had menstruated normally and had conceived a very short time after marriage. It is interesting to note that in the process of intercourse, which after a careful history, was found to be far from normal, the urethra had taken the place of the vagina and had become grossly dilated. In spite of the very small communication also the patient had become pregnant very shortly after marriage.

As regards future pregnancies, these should take place by the normal route with the usual precautions for a case of previous cæsarean section.

The second case is one of a septate uterus and a complete cervical and vaginal septum.

The patient, a primipara aged 23 years, was admitted as an emergency at the thirty-fourth week of her pregnancy with a history of slight vaginal bleeding for one week. Routine examination was normal except for the fact that the foetus was lying very obliquely with the head in the left iliac fossa. Now the history and clinical findings were very suggestive of placenta prævia and, as the pregnancy was only at the thirty-fourth week, it was decided to treat the case conservatively. The patient was kept in bed for four weeks during which time there was no vaginal loss. During this period soft tissue X-rays were taken but these were not conclusive one way or the other.

At the thirty-eighth week the patient was examined under anæsthesia in the theatre and a surprising discovery made. When the labia were separated a complete thick fleshy septum was found which was dividing the vagina into two. When a finger was introduced this septum was found to extend right up to the cervix, and with one finger in each vagina, two distinct cervixes could be felt. The one on the right side admitted a finger quite easily and through it a bag of water and a foetal head could clearly be felt. A finger-tip could also be inserted into the cervix on the left side and when it was withdrawn there was some blood present on the glove. It thus appeared at this stage that the patient had a double uterus and a double vagina with a pregnancy in the right side and that the bleeding had been coming from the non-pregnant horn. (Fig. 2).

Following this examination the patient was discharged home since it was decided to allow her to go into labour spontaneously at term should conditions remain favourable.

She was seen twice at the ante-natal clinic during this period and, since she had not gone into labour by the time she had reached her expected date, she was admitted to hospital to await labour in case any complication should occur when the pains commenced.

On the evening of 6th December 1947, the patient had one or two irregular contractions during the evening. I went to see her and found that the foetal head was still lying in the left iliac fossa and, what was much more disquieting, that the foetal heart was grossly irregular. She was taken to the labour ward at once and a vaginal examination carried out. The cervix on the right side could be felt and was found

to be fully taken up and about one to two fingers dilated. The membranes were still intact and a loop of cord could be felt coming down behind the head and pulsating very weakly. Theatre was called for at once but in spite of excellent work by certain members of the theatre staff, the foetal heart had disappeared before the operation could be commenced. The patient was therefore given a sedative and left.

During the night the uterine contractions improved and by noon the next day the cervix was fully dilated and the foetal head at the pelvic outlet. Beyond this it would not advance and delivery was expedited by craniotomy and extraction. During this procedure the vaginal septum was torn completely posteriorly and a portion was therefore excised. A hand was then introduced through the cervix, the septum of which had also been torn, and two fingers were passed into each uterine cavity. As far as could be made out there was only one uterus divided by a thick fleshy septum, and what had been considered to be two cervixes was again just one with a septum dividing it.

The patient's puerperium was uneventful and she was discharged from hospital on her tenth day. She was, however, re-admitted again last week for final examination. She was now found to have only one vagina but the scar where the septum had been was still visible. There was also only one cervix and a cannula was introduced through this and a quantity of neo-hydril injected. Under the screen this could be seen rapidly filling the left horn and before the right side filled there was considerable spillover on the left which has rather spoiled the picture. (Fig. 3).

To sum up, this case appeared at first to be one of two separate uteri, two separate cervixes and two separate vaginae, illustrating complete lack of fusion of the Müllerian system. However, after the final investigations I think that the uterus and cervix were divided by a septum and that the cervical one had been torn at the time of delivery. Thus partial fusion of the ducts had taken place at the upper end.

It is most unfortunate that this patient should have lost her baby. On account of the developmental abnormality and the associated oblique lie we were definitely on the look-out for prolapse of the cord, but she went into labour very incidiously and the foetal distress was extreme when it was diagnosed.

Before concluding I should like to thank Mr Band, the medical, theatre and ward staffs and Mr Shearsby and staff for their excellent co-operation with the treatment and follow-up of these patients.

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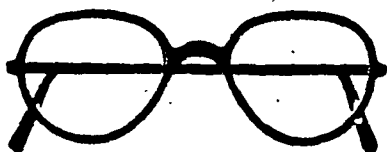
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# Edinburgh Medical Journal

*February 1949*

## DIET AND DENTAL HEALTH

By A. P. MEIKLEJOHN, M.A., B.Sc., D.M., M.R.C.P.

Lecturer in Nutrition, Department of Medicine, University of Edinburgh

IN the course of hospital practice we are constantly looking inside the human mouth and must often ponder the significance of what we see there. For a nutritionist, particularly, the mouth has many puzzles and especially, the teeth and gums. This was brought home to me, forcefully, when, in the winter of 1944-45, I visited France to collect information on the effects of war-time restrictions on nutritional health in that country. In Lyon and Marseille I examined a number of children who were clearly markedly undersized as a result of chronic underfeeding, and yet had much better dental health than most city children in Britain. In subsequent travels about post-war Europe I was constantly struck by the good state of dentition of children, despite frequent underfeeding, by comparison with our own. Schour and Massler (1947) have remarked that underfed children seen by them in Naples after the war had less caries than American children, and I am sure that many others who have seen people living on apparently poor diets in other countries, must often have been equally struck by finding remarkably healthy mouths. It looks, at first sight, as though there was almost a negative correlation between good dentition and good nutrition, and that teeth, like certain weeds, flourish best in a poor soil. A critical examination of existing knowledge on the subject may therefore be of interest.

In discussing dental health there are two quite separate pathological conditions to be considered, caries and parodontal disease (pyorrhœa, or chronic non-ulcerative gingivitis). They do not necessarily occur together: for instance, on the island of Tristan da Cunha the inhabitants have remarkably little caries, but more than a quarter have parodontal disease (Barnes, 1937), whereas the Pitcairn Islanders have healthy gums but severe caries (Cook, D. 1938). However, the two conditions very frequently occur together and both, ultimately, lead to loss of teeth.

A Honyman Gillespie Lecture given in the Royal Infirmary on 10th February 1949.



Caries and parodontal disease affect human health and happiness in the following ways :—

- (1) defective dentition may impair digestion ;
- (2) dental sepsis may result in bacteræmia ;
- (3) dental abscess may cause excruciating pain ;
- (4) the sight and smell of bad teeth are a social handicap and hence a cause of unhappiness.

This last, alone, is of sufficient importance to make poor dentition a serious matter.

In theory, the health of the teeth and gums may be influenced by the diet in two ways ; firstly, the local effects of foodstuffs in the mouth and secondly, the systemic (or metabolic) effects of nutrients necessary for their growth, maintenance and repair. It is convenient to consider the systemic aspects first.

## A. SYSTEMIC EFFECTS OF DIET

### (1) *Factors Influencing Calcification of Teeth*

The development of good dental structure is vitally dependent on the proper deposition of calcium salts (mainly phosphate) in the enamel and dentine during ante-natal and post-natal life. This calcification is influenced by the following factors :—

(a) *Dietary Sources of Calcium and Phosphorus*.—An adequate dietary intake of calcium is essential. Milk (as such, or in the form of cheese) is the most important source ; one pint provides about two thirds of a gram of calcium, the daily desirable allowance for adults and children being about one gram, with additional amounts in adolescence, pregnancy and lactation. Other sources include herrings, kale, beans and dried figs. In general, a diet containing sufficient calcium will also provide enough phosphorus.

Following the work of Sir Edward Mellanby, McCance and Widdowson (1942) showed that, in human subjects, the phytic acid contained in cereal grains partly inhibits the intestinal absorption of calcium and phosphorus, by forming indigestible salts with them. Oatmeal is apparently the most serious offender in this respect, although, when taken as porridge, the milk that goes with it usually provides more than enough calcium to offset the phytic acid ; nor should it be forgotten that in other respects, oatmeal is nutritionally superior to all other cereals.

During the battle of the Atlantic in the second world war, it became necessary in the United Kingdom to make the best use of imported wheat by including in the bread more of the whole grain than had formerly been the custom. On the advice of the Medical Research Council, the Ministry of Food raised the extraction rate of flour from 70 to 85 per cent. The resulting " National Loaf " contained more of the outer layers and germ (which were formerly fed to animals) and

therefore more calcium, iron, riboflavin and thiamin; but it also contained more phytic acid. To offset this, calcium carbonate is now added to the extent of 14 oz. to each 280 lb. sack of flour. This amount is more than sufficient to neutralise the phytic acid present in the bread and to make fully available its own content of calcium and phosphorus. The addition of calcium carbonate to bread has undoubtedly increased its calcifying properties.

(b) *Vitamin D*.—Vitamin D plays a vital part in calcification by facilitating the absorption of calcium from the intestine. In vitamin D deficiency the level of calcium in the blood plasma tends to fall. According to Allbright and his school (1946), a tendency to reduction in plasma calcium leads to increased activity of the parathyroid glands which stimulate the urinary excretion of phosphorus. Hence, as the plasma calcium tends to fall, there is an increased elimination of phosphates in the urine and the level of phosphorus in the plasma also falls. Since the deposition of calcium phosphate in teeth and bones is directly dependent on the level of these inorganic elements in the blood, vitamin D deficiency may result in dental decalcification.

The action of ultra-violet light on the natural precursor of vitamin D, 7-dehydrocholesterol, converts it into the active vitamin. This reaction takes place in the skin when exposed to sunlight. Hence sunlight may have important calcifying activity.

The parts played by vitamin D, sunlight and dietary sources of calcium in the prevention of rickets was first clearly demonstrated by the classic researches of Chick and her colleagues (1923) in Vienna after the first world war.

### (2) *Effects of Defective Calcification on the Teeth*

Rickets in infants results in late eruption of teeth, irregular spacing, mal-occlusion, poorly-calcified dentine and defective enamel. The results of poor calcification during the development of the teeth are shown in later life by the presence of dental hypoplasia. Gross hypoplasia ("G-hypoplasia") is easily recognised by pitting and irregularity of the enamel surface, usually affecting the incisors and often occurring in a definite band across them. Such hypoplasia is often referable to a severe infectious illness in childhood. A less well-recognised form of hypoplasia is that first described by Lady Mellanby (1934) and now called "M-hypoplasia." This is manifest by roughness of the enamel surface, not easily apparent on simple visual inspection, but readily detected by passing a fairly sharp probe over the buccal surface of the tooth.

### (3) *Poor Calcification and Susceptibility to Caries*

Lady Mellanby (1934, 1948) has shown that M-hypoplasia is associated with susceptibility to caries. Furthermore, she has proved beyond doubt that the administration of vitamin D to children of school age can result in a lower incidence of new caries than among

a comparable control group receiving no such supplement. It should be remembered that the teeth are constantly subject to attrition and repair ; though perhaps to a lesser extent than other structures in the body. An adequate calcifying diet is therefore probably necessary throughout life if the teeth are to remain healthy. But the crucial period in the life-history of a tooth is when it is first formed in infancy ; if, at this stage, the dentine has a well-formed matrix, properly calcified, and the enamel is uniformly dense, without flaws in surface continuity, the tooth has the best chance of remaining free from caries throughout life.

#### (4) *Factors Influencing Cellular Structures in Teeth and Gums*

(a) *Vitamin A*.—An important effect of vitamin A deficiency is to produce stratification and keratinisation of epithelial surfaces in many parts of the body. Such changes in the epithelium of the gums, affecting particularly the reflected surface in immediate contact with the tooth, might, in theory, result in a *nidus* for the accumulation of food particles and infecting organisms. It is quite uncertain, however, whether vitamin A deficiency is ever a factor in the development of human parodontal disease. The ameloblasts, which lay down the enamel in the developing tooth are of epithelial origin ; it is therefore theoretically possible that they might also be affected, and poor enamel result. But this does not seem to have been noted, particularly, in cases of infantile xerophthalmia described in the literature.

(b) *Ascorbic Acid*.—The classic description of scorbutic gingivitis was given by Lind (1753) who was born in Edinburgh in 1716 and took his M.D. here in 1748. In the first edition of his *Treatise of the Scurvy* the following description is given.

“ Their gums soon after become itchy, swell, and are apt to bleed upon the gentlest friction. Their breath is then offensive ; and looking into their mouth, the gums appear of an unusual livid redness, are soft and spongy, and become afterwards extremely putrid and fungus ; the pathognomonic sign of the disease.”

Ascorbic acid deficiency results in loss of intercellular cement substance and failure of collagen formation. The effect of these changes in the gums is to produce oedema and perhaps also actual increase in connective tissue, with capillary hæmorrhages. The interdental papillæ may be especially swollen (“scurvy buds”) and even protrude beyond the tops of the dental cusps. It is worth noting that secondary infection may contribute to the production of these changes. The remarkable experiment of Crandon, in which he induced scurvy in himself (Crandon, Lund and Dill, 1940) proved that a subject with good oral hygiene may develop scurvy without showing any characteristic changes in the gums.

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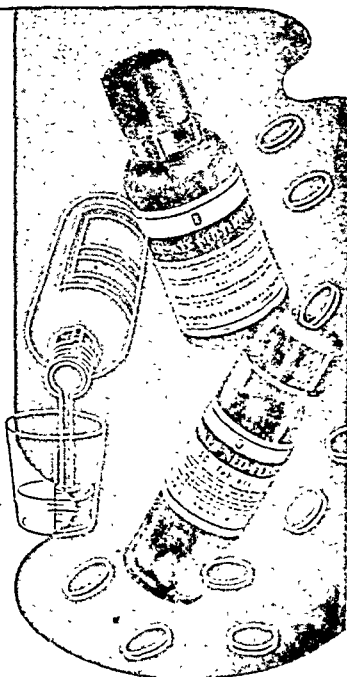
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The loss of collagen in the periodontal tissues between the teeth and their sockets results, after a time, in loosening of the teeth. The odontoblasts which lay down the dentine may be partly replaced by osteoblasts which, following recovery, may produce actual bone in the pulp cavity, known as "pulp stones."

(c) *Vitamin B Complex*.—There are no characteristic changes in the teeth or gums in the classical syndromes associated with deficiency of the vitamin B complex. King (1940a) has claimed benefit from oral nicotinic acid in the treatment of "trench mouth" (Vincent's disease); but this is most likely to be a non-specific pharmacological effect, since his patients were scarcely likely to be deficient in this vitamin.

#### (5) *Protection Against Caries—Fluorosis*

Since 1931 it has been recognised that the presence of fluorides in drinking water results in certain characteristic changes in the teeth, known as fluorosis. Such changes begin to be noticeable in districts where the water supply contains over one part per million of fluorine. Where the water contains as much as 10 parts per million of fluorine, most of the inhabitants will have severe fluorosis. In mild cases, the only change is that of scattered china-white flecks ("mottling") in the enamel of one or more teeth. The recognition of mottled enamel sometimes gives an unexpected clue about a patient. In Germany last spring I found that I could often identify children who were refugees from the Russian Zone by their mottled teeth. In severe cases every tooth may be affected; instead of a mottled appearance, the whole surface of the enamel may be china-white, lacking the usual glazed, translucent appearance of normal enamel. In addition, the enamel surface may be deformed by pitting, somewhat resembling gross hypoplasia. The third change in severe cases is a brown staining of the enamel, particularly noticeable near the gum margins. Such fluorotic teeth may be unusually soft; they are frequently faceted on the biting surfaces and worn-down by attrition, and yet they are remarkably resistant to caries. Surveys in many parts of the world have shown beyond doubt that fluorosis is associated with a reduction in caries incidence; this is further discussed below under endemiology of caries. It has been shown that mottled teeth contain more fluorine than teeth from individuals free from mottling. The current view is that fluorine exerts its protective action by a local effect on the bacterial flora surrounding the teeth.

### B. LOCAL EFFECTS OF DIET ON TEETH AND GUMS

(1) *Food Particles Lodged Round the Teeth*.—A German visitor to the Court at the Royal Palace of Greenwich in the year 1598, left a personal impression of Queen Elizabeth; he commented on her hooked nose, narrow hips and bad black teeth: "a defect the English

seem subject to from their too great use of sugar" (Drummond and Wilbraham, 1939). The belief that refined sugar may have a deleterious effect on the teeth is therefore venerable. The free use of sugar, however, did not become general until the nineteenth century, when renewed interest in this belief was awakened by the rise of bacteriology, which at first seemed to show that every human ailment would ultimately prove to have an infective origin. It was demonstrated that saliva from patients suffering from caries was capable of fermenting sugars with the production of acids that could dissolve the enamel of extracted teeth. The possible influence of acid-forming bacteria in the mouth has been a subject of interest ever since. The principle organism concerned is the *Lactobacillus acidophilus* and it now seems established that the addition of sodium fluoride to culture media will inhibit the production of acids by this organism and that its presence in drinking water reduces the numbers of lactobacilli found in the mouths of children, (Dean, Jay, Arnold and Elvove, 1941). But it has yet to be shown that this is the explanation of the unusual resistance of fluorotic teeth to caries.

There have been repeated experiments which seem to indicate that the addition of refined sugar to children's diets increases the incidence of new caries (see for instance the recent work of Whyte (1945) in Dundee); but not all writers agree with this (King, 1946) and argue that, in the earlier experiments at least, insufficient precautions were taken to see that the diet had adequate calcifying properties.

(2) *The Flow of Saliva*.—The flow of saliva is stimulated by the sight, smell and taste of food. In theory at least a dull, dry diet might limit or modify the salivary flow and so facilitate the accumulation of food particles and tartar on the teeth. Tartar is composed of calcium salts, mucin and bacteria; remarkably little is known about its origin or cause. Its deposition is aided by such mechanical factors as mouth-breathing and mal-occlusion and probably begins in pockets formed between the gums and the tooth surface; it is possibly true that such deposits do not occur if the gums are perfectly healthy. Whatever the causation of tartar, it seems safe to say that it is not likely to be due to psychoneurosis as is suggested in the 1940 edition of one textbook on dental diseases!

(3) *Infective Organisms in the Food*.—Bacteria capable of infecting both teeth and gums may gain entrance to the mouth in the food. This is illustrated by ulcerative gingivitis (Vincent's disease) which tended to occur with special frequency among officers and particularly air-crews, during the second world war. This gave rise to the suspicion that its spread was associated with the sharing of eating utensils. Although it is not fashionable at the moment to lay much stress on the element of infection in the production of caries and paradontal disease, this should not be overlooked; it may yet prove to be an important factor in the development of caries in people who migrate from rural life to settle in towns.

(4) *Mechanical Factors*.—There has been a recent revival of interest in the possible influence of purely mechanical factors in the preservation of the health of teeth and gums. Primitive people usually have to do a good deal of chewing before they can swallow their food; the Eskimo woman chews seal-skin between meals, in order to make it soft (Pedersen, 1947). On the other hand the diet of the city-dweller in Britain and America, consisting of soft, machine-milled bread and well-cooked foods, needs little chewing. In the words of Fish (1944): "among civilised people on a soft diet, the teeth are not worn down, and the epithelium of the gum margins gets very little friction. The surface of the epithelium becomes soft, and is easily cut or torn by occasional sharp particles of food. These cuts and tears develop into chronic marginal ulcers since they get no opportunity of healing."

It has been observed that the natives of Jamaica have excellent gums; they very frequently chew sugar-cane which, despite its high sugar content, may help to protect the gums by providing massage. The chewing of sugar cane has recently been tried in the treatment of parodontal disease in English boys (King, 1947). The possible influence of "disuse odontoporosis" should not be forgotten (Neumann, 1947). There seems, however, to be no evidence that the American habit of chewing gum has any beneficial effect on the teeth and gums.

### ENDEMOLOGY OF DENTAL CARIES

Dental caries occurs among people of British ancestry throughout the world and among other people who have been persuaded to adopt their dietary habits. Rickets used to be called "the British disease" and caries has at least as much title to that name. It is rare among aboriginal races who have preserved their native dietaries. There is good reason for thinking that the incidence of dental caries among the British was not always so severe as it is to-day; for instance, among skulls preserved in the vaults of St Leonard's Church, Hythe, about half had not lost a single tooth before death, although many were not of young people as shown by the polished surfaces of their well-worn teeth (Drummond and Wilbraham, 1939). These skulls date from the period between 1250 and 1650. During the nineteenth century, however, the incidence of caries in Britain appears to have increased at an alarming rate until, at the end of the century, a national scandal was created by the rejection of 40 per cent. of recruits for the South African war, largely because of bad teeth. It is at least plausible to suggest that this increase in caries was connected with the reduction in consumption of milk, the increased consumption of sugar and the introduction, in the 1880's, of roller-milled white wheat flour which was softer and less nutritious than the traditional whole-meal stone-ground wheat or rye.

The present distribution of caries throughout the world offers an opportunity to consider the influence of various kinds of diet in its



production. Before passing on to such considerations, it is necessary to remember the factor of fluorosis.

*Fluorosis and the Distribution of Caries.*—Numerous surveys have now established that the incidence of caries is unusually low in localities where the water supply contains one part per million or more of fluorine. This was demonstrated in the U.S.A. where surveys by McKay (1948) and Dean *et al.* (1942), among others, have shown a close correlation in many localities between the fluorine content of the water and reduction in the numbers of decayed, missing or filled teeth (DMF index).

Shourie (1946) in India has demonstrated that the presence of fluorine in drinking water in the Punjab is associated with mottling and a lower incidence of caries by comparison with Madras State. There is possibly an extension of this "fluorine belt" along the north shore of the Persian Gulf; I have personally seen a high incidence of fluorosis among men from certain parts of this area. I also encountered an interesting local incidence of fluorosis in Italy in a village north of Rome (Compagna di Roma) associated with virtual absence of dental caries. It should be noted that there are reasons for thinking that fluorosis is particularly likely to be manifest in mal-nourished people (Wilson, 1941).

In England, a remarkable demonstration has been made by Weaver (1944) in the towns of North and South Shields; these are really a single town, divided only by the River Tyne, without any important differences in the social or economic circumstances of the inhabitants; but they have separate water supplies. The water in North Shields contains 0.25 part per million of fluorine and the DMF index among twelve-year-old children there is 4.3 on average; while in South Shields the water contains 1.4 parts per million of fluorine and the DMF index in children of the same age is only 2.4.

The highest fluorine-content thus far found in British water supplies is 5 parts per million in Malden in Essex. This is associated with a very high incidence of fluorosis and a low incidence of caries (Bowes and Murray, 1936). The whole subject has been extensively reviewed by Roholm (1937); a useful summary is to be found in the recent Medical Research Council report (1949) on fluorosis at Fort William. This report mentions that the highest incidence of fluorosis in Scotland appears to be in Roxburgh, and the lowest in Angus.

The deliberate addition of fluorine, to the extent of one part per million, to water supplies is now being tried out in at least 5 different cities in North America (*Nutrition Reviews*, 1947). If this experiment proves successful, it may ultimately make a profound difference to the distribution of dental caries throughout the world. Encouraging reports have also appeared in America on the beneficial results of periodic local applications of fluorides to the teeth (see for instance, Bibby, 1947). It is necessary to remember, however, that the ingestion

of fluorine in unusual amounts may result in serious bony deformities (Murray and Wilson, 1942).

*Diet and the Distribution of Caries and Parodontal Disease.*—There have been a number of studies of dental health in relation to the diet of peoples throughout the world. The following are some examples.

The classic study of Orr and Gilks (1931) in Kenya, demonstrated the remarkable difference in the incidence of caries in two populations with different dietary habits; the Masai—a violent and feckless tribe—live almost entirely on meat, milk and raw blood: an exclusively carnivorous diet like that of the gauchos of South America and the Tartars of old. They have remarkably little dental caries. A recent survey (Schwartz, 1946) found only about 40 carious teeth among over 400 adults; but the great majority suffer from parodontal disease and tartar. The Kikuyu, on the other hand, industriously cultivate millet, maize, sweet potatoes and yams which provide a diet on which their children develop frequent rickets and a greater incidence of caries (13 per cent. among the children).

An interesting account of the dentition of Greenland Eskimos has recently been given by Pedersen (1947). Dental caries is practically non-existent among these people in their native state; the examination of over 500 skulls revealed only two with caries. But severe caries has developed among those who have come in contact with coastal trading stations and have tasted, for the first time, sugar and white bread in place of their traditional diet of seal meat. No fluorosis was observed among these Eskimos except among those living near a cryolite ( $\text{Na}_3\text{AlF}_6$ ) mine and among the children of mothers who had formed the extraordinary habit of mixing cryolite with their snuff. Among old Eskimos of both sexes the teeth are often worn down to the gums, though without any sign of decay. It is interesting that multiple small fractures of the teeth and large pulp stones are frequent; both changes suggest previous ascorbic acid deficiency, which is not surprising considering the nature of their diet. I believe that, apart from the minute amounts provided by meat, almost their only source of ascorbic acid is blaeberrries, which they eat in prodigious quantities during the brief season. Possibly attributable to the same cause is the widespread incidence of gingivitis.

Mention has already been made of the inhabitants of Tristan da Cunha. They are people of British ancestry who, on a diet composed mainly of fish, potatoes, milk and eggs, were remarkably free from caries. But the recent importation of white flour and sugar and, incidentally, tooth brushes (Drummond and Wilbraham, 1939) has been associated with an increase of caries. At least one quarter of the inhabitants suffer from parodontal disease, perhaps because their diet contains no source of ascorbic acid except potatoes. By contrast, the Pitcairn Islanders eat plenty of fruit and are said to have healthy gums.

In India generally, people living in primitive rural communities are remarkably free from caries although they often suffer severely from parodontal disease. But among the wealthier urbanised populations, who have adopted westernised dietary habits, caries is common (Passmore, R., personal communication).

In general, caries appears to be less common in sunny climates, quite possibly because of the effect of sunlight in promoting the synthesis of vitamin D in the skin. The incidence of caries in the U.S.A. is doubled in passing from the Gulf of Mexico to the Canadian border (Mills, 1937).

Coming nearer home, a detailed survey by King (1940*b*) on the Island of Lewis has shown that the incidence of caries among the rural population is lower than in the town of Stornoway. This appeared to be associated mainly with a greater consumption of milk, fish and oatmeal in the country districts. The use of white flour and sugar was much the same in town and country. King showed a close relation between the incidence of caries and M-hypoplasia and lays stress on the higher calcifying properties of the rural diet. The incidence of parodontal disease was about the same in both groups of children; about one per cent. in the age group 13-15. This is higher than in London and raises the question whether the high consumption of potatoes in Lewis is sufficient to offset the low consumption of fruit and vegetables as a source of ascorbic acid.

*Personal Observations in Urban Britain.*—There can be no question that both caries and parodontal disease are excessively common among the present urban population of the British Isles. In the course of a series of nutrition surveys which I carried out for the Ministry of Health in 1942-43, I examined a random sample of about 100 adults, of average age about thirty, in each four industrial areas (Accrington, Merthyr Tydfil, Chesterfield and Dundee); only about one quarter of the sample in each locality had a sufficient set of teeth remaining, free from visible caries. The incidence of obvious parodontal disease ranged from 18 per cent. in Merthyr to 33 per cent. in Dundee.

*Parodontal Disease and Ascorbic Acid Deficiency in Dundee.*—In four women seen in Dundee, the gums were swollen and livid as well as inflamed, suggesting the appearance of scurvy; the suspicion that ascorbic acid deficiency might be concerned, was confirmed by the subsequent finding that two of these women were the only subjects, out of 63 tested, with no measurable amount of ascorbic acid in the plasma. In the other two subjects the plasma level was so low as to be barely measurable.

In considering the possible relation of parodontal disease to low levels of ascorbic acid in the plasma, the factor of poor oral hygiene must be remembered. Carious teeth and accumulations of tartar may predispose to parodontal disease, and people whose mouths are in a neglected condition are just those people who are likely to eat an unbalanced diet, poor in ascorbic acid. However, in the case of my

observations in Dundee the factor of oral hygiene did not seem to be important because even in subjects with clean mouths, the average level of ascorbic acid in the plasma was apparently lower in those with parodontal disease than in those without.

It is of interest that Professor Gordon Campbell and Dr Cook (1942) had previously reported beneficial therapeutic results from large doses of ascorbic acid to patients with certain forms of gingivitis in Dundee. It is understandable enough that ascorbic deficiency should be found in Scotland, in view of the scarcity of fruit and the usual recipe for cooking vegetables in broth: "boil till all the vitamin is destroyed, then serve."

*Recent Changes in the Incidence of Caries—Effects of the War Years.*—There is some evidence that the tide is beginning to turn in the appalling incidence of caries which grew up in the British Isles in the nineteenth century. The careful surveys of Lady Mellanby and her colleagues (1948) of five-year-old London children, have shown a steady improvement in the incidence of caries and of M-hypoplasia during the war years and after. This improvement they attribute to the better calcifying properties of the diet of both infants and their mothers resulting from the addition of vitamin D to margarine, of calcium carbonate to the bread and, particularly, to the priority allowances of milk, cod-liver oil and eggs to mothers and their infants.

## DISCUSSION

Returning now to the starting-point of this lecture: how are we to explain the good state of dentition of underfed French children liberated in 1944?

Firstly why was there so little caries? On the evidence of Lady Mellanby it is reasonable to conclude that the basic structure of their teeth was sound. This structure would have been laid down in infancy and even pre-natal life, at a time preceeding the food restrictions imposed by military occupation. This surely, is the essential lesson; that when we examine teeth we are often observing the effects of the diet remote in time from the present. The dietary factors that result in good dental structure are those that promote good calcification; the examples quoted from Kenya, the U.S.A., Lewis and London suggest that the principal factors are vitamin D or sunshine and, especially, milk.

In some communities fluorosis is important in giving protection against caries, although among the French children this was not evident.

When we come to the question of local effects of foodstuffs promoting dental caries by direct contact with the teeth we are on much less certain ground. But the experience among the Eskimos, in India, Tristan da Cunha and historically, in Britain, can leave little room for doubt that there are deleterious factors in the fancy, refined dietaries

of western urbanised life : factors that provide the over-rich soil on which the teeth decay. It may yet be that refined foods, and especially sugar, are important causes of the caries that daily confronts us. Certainly in the case of the French children and others, such as those of the Channel Islands (Knowles, 1946) and of Norway (*Lancet*, 1946), where dentition improved during German occupation, sugar was not a notable feature of their diet.

Coming now to parodontal disease : the French children had excellent gums, perhaps because they had been living on rough, whole-meal bread with abundant vegetables providing a high intake of ascorbic acid ; though underfed (lacking calories), there was no evidence that they were mal-nourished (lacking specific nutrients).

Elsewhere, however, parodontal disease, in contrast to caries, has a wide distribution, even among people in isolated rural communities living on their traditional diets. The factor of trauma has been stressed, on gums grown unresistant by easy eating of soft, luxurious foods. The question for the nutritionist is, what systemic factors delay the healing of the trauma, once it is there ? The evidence of Campbell and Cook (1944) and the personal observations given in this lecture, suggest very strongly that, at least in Scottish urban communities, ascorbic acid deficiency is a cause of delayed healing and so, of persistent parodontal disease. The same may also be true among other peoples whose consumption of this vitamin is low, such as the Massai, the Eskimos, the inhabitants of Tristan da Cunha and, possibly, those of the island of Lewis. In Germany, certainly, parodontal disease in children seemed more common, following the potato and vegetable shortage of last winter (Meiklejohn, 1948). We should not be deterred by reports, chiefly from America, that ascorbic acid produced no benefit in parodontal disease among people whose intake of this vitamin is obviously adequate ; clearly, among such people, ascorbic acid deficiency cannot be a causative factor. But among people with a low dietary intake of the vitamin, the administration of ascorbic acid tablets is surely a logical accompaniment to the local treatment of parodontal disease.

### CONCLUSION

Much is already known about the relation of diet to dental health. Some of the broad issues are already clear ; but there is much still to be learnt. It should not be forgotten that there are still dietary factors of which we have little or no knowledge, and these may ultimately prove to be important for dental health. More research is urgently needed, especially into the endemology of caries and parodontal disease, defining more precisely the incidence of these conditions in different kinds of community in relation to present and past dietary habits.

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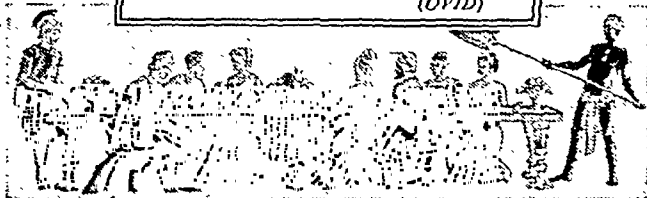
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the rising tide of dental caries. It may have arrested, but it has certainly not abolished parodontal disease. As a nutritionist, I cherish the hope that through better knowledge of nutrition, the ward visit of the future may be cheered by the clean white smiles of the patients.

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# THE EXPERIMENTAL AND CLINICAL USE OF ANTIHISTAMINE DRUGS

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HISTAMINE is a normal constituent of living tissue. It is, however, held there in an inactive form and will only produce its profound pharmacological effects if released as free histamine. We are still uncertain of the part this tissue histamine plays in normal physiological processes but because of the similarity of the effects of injected histamine and some of the manifestations of allergy, it has been considered likely for thirty years that in the allergic state a release of histamine occurs as a result of the union of antigen and antibody within the tissues of the individual.

In animals it has been conclusively proved that histamine is released from the tissues during anaphylaxis, and the drug is in large measure responsible for the manifestations of this condition (Bram Rose, 1947), (Gaddum 1948). In man the evidence that such a release of histamine occurs in the allergic state is by no means conclusive but there is a large body of circumstantial evidence which makes this a most likely hypothesis. It has been demonstrated that there is a release of histamine from the skin when an antigen to which the patient is sensitive is brought in contact with it. It has also been shown that when the blood of a hay fever subject is mixed with the allergen, there is a release of physiologically active histamine from the white blood cells. The classical experiments of Lewis (1927) drew attention to the marked similarity between naturally occurring urticaria and the weal and flare which result when histamine is injected into the skin. In contrast, however, to the ease with which histamine can be removed from the artificially produced weal, no one has so far been able to extract histamine or a histamine-like substance from the natural urticarial weal.

In some allergic individuals who are sensitive to cold there is a marked similarity in the reaction which results on exposure to cold and the effects produced on the injection of histamine including a flow of gastric hydrochloric acid. But it has never been proved that it is histamine which gives rise to this reaction, and in conditions such as asthma and urticaria attempts to detect significant changes in the blood and urine content of histamine have not been very successful.

In assessing these negative findings, the behaviour of histamine in the body and the peculiar difficulties attending this type of research work should be noted. It is probable that the amounts of histamine involved in human allergic states are much less than in anaphylaxis in animals. It is also known that not only is histamine rapidly removed from the blood stream, but amounts of histamine large enough to produce pharmacological responses are not always detected by the methods at present in use.

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Adam and Hunter (1948) have conducted a number of experiments in which they infused 5000 microgrammes of histamine intravenously over a period of four hours. Even when the histamine was given sufficiently quickly so as to produce vomiting and collapse, they were unable to detect any increase of histamine in the blood plasma of these patients; the histamine doubtless having been rapidly removed from the blood stream and stored in the tissues. There was, however, in these cases an increased output of histamine in the urine (Adam, 1948).

It is probable then that in allergic states histamine is released, but the amounts involved must be small and any reaching the blood stream is quickly removed from it. From the experiments of Adam and Hunter, examination of the urine would be the earliest method of detecting a release of free histamine in the body, because its presence is evident there before there is any increase detectable in the plasma.

There are other observations on the effect of parenterally administered histamine which are important. When the drug is administered to man by intravenous injection, the earliest and most predominant effect is on blood vessels leading to profound vasodilation (Weiss, 1932). This is in contrast to many experimental animals in which the predominant effect produced is spasm of plain muscle. It has also been noted in man that whereas in the healthy subject this administration of histamine does not produce broncho-spasm, in the asthmatic subject bronchospasm is produced and the degree of spasm is in direct proportion to the clinical severity of the asthma (Curry, 1946). It seems that in such persons there is an idiosyncrasy to histamine which is evident only in the part of the body affected.

In other experimental histamine studies it has been noted that antihistamine drugs will prevent the effects of parenterally administered histamine including the histamine produced bronchospasm in the asthmatic though they have little effect in relieving naturally occurring bronchospasm (Curry and Lowell, 1948). They are also without effect on the histamine-induced flow of gastric hydrochloric acid.

The discovery in 1937 by Bovet and Staub that certain substances would antagonise the action of histamine marks the beginning of a new era in the therapeutics of allergic disorders. The first antihistamine drug was called thymoxy ethyl diethylamine, but it unfortunately proved to be very toxic. Experimental work with similar compounds continued and it was found that substances containing an ethylene diamine radicle were less toxic (Staub, 1939). The most potent antihistamine of this group was 1571 F., but it also proved to be toxic and after an abortive clinical trial its use was abandoned.

The drug antergan was introduced by Halpern in 1942 and proved to be a potent and specific antihistamine drug sufficiently non-toxic to allow of its clinical use. Bovet introduced neoantergan in 1944 and the drug has been marketed in this country under the trade name of Anthisan.

It is a tribute to the workers of the Pasteur Institute in Paris that the work culminating in these discoveries was carried out during the

German occupation. Because of the war these discoveries did not become generally known for some time, but reading the French clinical literature of that period, there is no doubt that the therapeutic possibilities of these drugs were quickly realised and they were used widely in the treatment of allergic disorders.

In 1945 two antihistamine drugs were introduced in the United States of America, benadryl (Loew *et al.*, 1945), and pyribenzamine (Mayer *et al.*, 1945). Benadryl is a benzhydryl ether and pyribenzamine is so closely related to anthisan as to expect a close similarity of action. Experimental and clinical studies have proved this to be so.

Since 1945 at least a dozen other antihistamine drugs have been produced. The majority are derivatives of antergan or anthisan, but as few of these substances have yet received extensive clinical trial and none have proved their superiority over anthisan, the only one which shall be referred to further is antistin because it has recently become available for clinical use in this country. In its structure it is closely related to antergan.

PHARMACOLOGY.—Some brief reference has to be made to the pharmacology of these drugs to understand their possible therapeutic uses and also their limitations. A large number of careful antihistamine studies have clearly shown that anthisan is the most potent and specific antihistamine drug. It has also been shown that the drugs act by blocking the tissue receptors for histamine thereby preventing histamine from producing its customary effects (Halpern, 1946). This means that the production of histamine and the allergic state which is giving rise to its release are not directly influenced.

All members of this group of drugs have properties other than their antihistamine action. The two properties which are important are a local anæsthetic action and an anti-acetyl choline effect. They have other actions as well but these are more of interest to the pharmacologist than the clinician. Of all the antihistamine drugs anthisan has the least anti-acetyl choline effect (Schild, 1947), making it the most suitable drug for experimental study. Benadryl and antistin have both considerable atropine-like properties. This is evidenced by the dryness of the mouth which benadryl frequently produces.

Lewis noted many years ago that local anæsthetics would modify significantly the histamine skin weal and it has been shown that antihistamine drugs also have this effect. The question arises whether this is due to a local anæsthetic action or the antihistamine effect of the drug. The problem has been considerably clarified by the work of (Code *et al.* 1948), who studied the relationship between the local anæsthetic and antihistamine properties of the drugs on the skin. He found that the effects were independent of one another. Drugs with the strongest local anæsthetic action were the weakest antihistamines and he also noted that the antihistamine effect persisted after the local anæsthetic action had worn off.

The reduction of the weal is easily explained by the local action of

the antihistamine drug blocking the histamine receptors. But the reduction of the flare is not so easily explained. As the production of the flare depends on the integrity of nervous pathways it is likely that antihistamine drugs produce this effect by an action on nervous tissue. It is not necessary to postulate a different site of action from local anæsthetics but only a slightly different effect on the same tissue.

Antihistamine drugs therefore have an action on nervous tissue in the skin resulting in a diminution of the flare response when histamine is injected. This result is also produced when the drugs are given by mouth and under these circumstances no anæsthesia of the skin can be detected.

It has been thought for many years that histamine was concerned in the production of cutaneous pain and itching but at the same time it was realised that this could not be the whole answer (Rothman, 1941). The quantities of histamine required to produce itching on injection will also produce weal formation, though it does not produce pain. A recent contribution by Emmelin and Feldberg (1947) throws light on this problem. They discovered that a nettle sting contains histamine 1/1000 and acetyl choline in a concentration of 1/100. Either of these drugs injected alone is relatively painless but when injected together they will produce itching and a severe burning pain. It seems reasonable to postulate that cutaneous pain and itching are due to the release of both these substances. The fact that anthisan is a potent drug in relieving itching suggests that it acts by upsetting the histamine acetyl choline partnership. Benadryl has been found by some to be a more potent drug in the treatment of itching skin conditions and in this connection its anti-acetyl choline effect may be an additional advantage.

**ADMINISTRATION.**—Benadryl and pyribenzamine are usually prescribed in doses of 50-100 mgm. and anthisan and antistin in doses of 100-200 mgm. The limiting factor in giving larger doses is the severity of side effects which become more frequent when higher dosage is given.

The drugs are quickly absorbed and in large part excreted within four to six hours. Because of this, they have to be administered three or four times a day and in some cases it is necessary to give an additional dose late in the evening to prevent a recrudescence of an allergic disorder during the hours of sleep. Children tolerate antihistamine drugs very well and over the age of twelve can be given the adult dose, with proportionately smaller doses under that age. As all the drugs are potent, local anæsthetics, tablets or cachets should be swallowed and not chewed because they give rise to an unpleasant numbness of the mouth which will last for some time.

We are not sufficiently experienced in the parenteral administration of antihistamine drugs to be able to assess their value and also this route of administration is not without danger. Its only certain justification at the moment is in anaphylactic episodes in man. In the

majority of allergic disorders because of the rapid absorption of the drugs, the oral route is the method of choice.

### THERAPEUTIC APPLICATIONS

**CHRONIC URTICARIA AND ANGIO-NEUROTIC ŒDEMA.**—The beneficial results of administration of antihistamine drugs is best illustrated by their use in urticaria. In most of our studies in this condition and in other allergic states we have used anthisan because it is the most potent and specific drug.

Within half an hour or so of administering the first dose of an antihistamine drug to a case of urticaria, there is a diminution of itching and this is followed by a decrease of the number of lesions appearing. As would be expected by the mode of action of these drugs, they have little or no effect on established lesions which will spontaneously subside. It is for this reason that treatment with adrenaline is still required when there is œdema of the tongue and glottis. Initially the drugs are given three times a day and the quantity given, and the number of doses increased until full control of the allergic state is established. Thereafter when the condition has been controlled for some time, the daily dose can be gradually reduced till the minimum amount of the drug required to control the allergic state is established.

Antistin has not proved very effective in urticaria, but there is probably no great difference in the efficacy of the other preparations which will control over 80 per cent. of cases. Antihistamine drug treatment should never be terminated suddenly in these cases because the allergic state may manifest itself more violently than before. This rebound phenomenon has also been observed in experimental histamine weals in the skin.

Increased tolerance to antihistamine drugs does not seem to occur, in fact in the majority of our cases the requirement of the drug gradually becomes less. This suggests that either the allergic tendency is subsiding, or that spontaneous desensitisation is occurring under the protection of the drug.

**ACUTE URTICARIA.**—When this is due to drugs such as sulphonamides, penicillin and insulin, the administration of antihistamine drugs has proved of benefit. It is important, however, to realise their limitations in the treatment of drug reactions. There is no proof that they markedly alter a toxic reaction unless it is urticarial in type. This is well illustrated by the serum sickness type of reaction which occurs with penicillin. In this condition, though there is disappearance or a considerable modification of the urticaria, the pyrexial reaction is little modified and the joint pains and the duration of the illness are in no way altered.

**PRURITUS.**—The dramatic relief which is afforded to many patients with itching skin conditions would be sufficient reason in itself for introducing antihistamine drugs as therapeutic agents. Reports in the literature vary as to their effectiveness. Taking the whole range of

itching skin conditions, probably only about 15-20 per cent. of cases receive marked benefit from the drugs. Where there is evidence of an allergic basis, the percentage is much higher and in urticarial lesions approaches 80 per cent. Hunter and Dunlop (1947) have reported the marked relief which they afford in the pruritus of obstructive jaundice—a relief which may obviate the necessity of a palliative cholecyst-gastrostomy. In pruritus vulvæ and in pruritus ani they are also of marked benefit. Reference has already been made to their probable mode of action.

**LIVER SENSITIVITY.**—There is no doubt that antihistamine drugs have a place in the management of liver sensitivity. It is equally important to realise their limitations and not all cases are benefited. Hunter and Hill (1947) have found that the threshold of sensitivity to liver in the skin is an important guide.

When the threshold of liver sensitivity is high, antihistamine drugs do not modify materially the severity of the reaction. These cases are best treated by cautious desensitisation under cover of full doses of antihistamine drugs and adrenaline as well. Probably in sensitive cases a large quantity of histamine is released as well as other tissue cleavage products and the small quantity of antihistamine drug present is quite unable to cope with the magnitude of the reaction.

**HAY FEVER.**—Results with antihistamine drugs in hay fever are so encouraging that they are replacing desensitisation therapy in its treatment. The swallowing of a few tablets in the day during the hay fever season is sufficient in about 75 per cent. of cases to reduce the rhinorrhœa sneezing and nasal blockage to a trifling inconvenience. In the remaining cases they are without effect and the older treatment has to be resorted to. In very severe cases of hay fever, a course of desensitising injections followed by the administration of antihistamine drugs during the season has led to complete absence of symptoms in 95 per cent. of cases.

It is important to note that desensitisation therapy should not be carried out under cover of antihistamine drugs. Reactions may be delayed but just as severe. There is always the temptation also to give bigger doses of pollen extract under the protection of antihistamine drugs. This should be avoided.

**PERENNIAL RHINITIS.**—Results in this condition do not appear to be so clear cut as in hay fever. Benadryl particularly has proved itself disappointing. One reason for the varied reports is that due attention has not been paid to the local condition of the nose, and when sepsis and large polypi are present they should be attended to before drug treatment is instituted.

Reid and Hunter (1948) have recently studied a series of rhinitis cases. They selected cases with uncomplicated rhinitis, all of which had had symptoms for six months and all of whom had an allergic nasal mucosa.

The cases were given anthisan 0.6 gm. in the day after a fortnight on dummy tablets. During the control period it was noted that 35

per cent. of cases had some relief of symptoms, but their nasal appearances were little if at all altered. In two cases the condition spontaneously subsided. These findings suggesting that psychological factors play a big part in this condition. After the active drug had been given for a period of a month 51 per cent. of cases had complete symptomatic relief with reversion of the allergic nasal mucosa to normal. More than half these cases were symptom free three months after treatment was stopped.

**ASTHMA.**—The therapeutics of asthma has always been the home of the uncritical therapeutic enthusiast. The suggestibility of the patients and the spontaneous fluctuations in the condition, make it easy for the hopeful to find good in almost any remedy. Realising the pitfalls, we have recently attempted to evaluate antihistamine drugs in the treatment of this condition (Hunter and Dunlop, 1948). We chose young people without complicating sepsis and all of whom had an allergic family history as well as other personal evidence of allergy such as hay fever, urticaria or a history of infantile eczema.

There were 32 patients in this group and they were observed for nine months. During the first three months they had no routine treatment other than with sympathomimetic drugs. During the second period some had dummy tablets and some had anthisan, and during the third period those who had had anthisan were given dummies and the others anthisan. In each of these three periods the number of asthmatic attacks were carefully recorded. Reading the records of the number of attacks while on anthisan, there were 11 cases—34 per cent. who appeared to be markedly benefited. However, when the records of the control periods were examined, it was noted that in 8 of the cases there was as great, or greater improvement, with the inactive tablets as with anthisan. In the 3 cases which appeared to benefit, the improvement was not maintained in any of them during a further period on anthisan. As a result of this study, it was concluded that anthisan had not proved its value in the treatment of asthma.

**MISCELLANEOUS CONDITIONS.**—We have treated a number of cases of periarteritis nodosa allergic purpura and migraine and not observed any benefit. One case of scleroderma and one of dermatomyositis were quite uninfluenced by treatment. X-ray sickness does not benefit from the administration of antihistamine drugs (Court Brown and Hunter, 1949). In alimentary allergy the evidence is increasing that they may produce remarkable benefit.

**SIDE EFFECTS.**—A single dose of 100 mgm. benadryl will produce side effects in 50 per cent. of cases (Feinberg, 1946), and in our experience antistin will produce side effects in about the same frequency. With anthisan and pyribenzamine a single dose of 200 mgm. will produce side effects in over 30 per cent. of cases.

With all the antihistamine drugs there is a tendency for the side effects to wear off and if a small dose is given initially and the daily amount gradually increased, the side effects will be minimised.

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Drowsiness, fatigue and nausea are the commonest effects with all antihistamine drugs. The drowsiness can be minimised by the administration of amphetamine 5 mgm. in the morning and again at mid-day. Its administration need only be continued for a few days till tolerance to the side effects has been achieved. It is contraindicated when tension present. Because of the sedative effect of the drugs, care has to be taken in the coincident administration of hypnotics, and as this side action may be marked after the first dose, it is best taken at night and should never be taken before performing work requiring skilled judgment such as driving a motor car.

Nausea and vomiting are more common with anthisan and pyribenzamine than benadryl, and can be minimised by always giving the drug immediately after a meal, or if at other times, together with a cup of milk or a biscuit. Because of the atropine-like effects of the drugs, particularly benadryl, the coincident administration of atropine or its derivatives is best avoided. There is no contraindication to the administration of sympathomimetic drugs, in fact they may be an additional advantage in cases ill controlled by antihistamine drugs.

Antihistamine drugs are remarkable in that there is an unusual absence of toxic effects leading to death or serious tissue damage, in fact during the five years of their use, no deaths have been reported.

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# AN ESSAY ON THE REACTIONS OF THE MESEN- CHYME WITH ESPECIAL REFERENCE TO THE "RETICULOSES"

By HELEN RUSSELL, M.D., F.R.C.P. EDIN.

Pathologist to the Christie Hospital and Holt Radium Institute,  
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IN teaching post-graduate students to-day certain difficulties have been found in correlating their memories of the pathology of the acute, sub-acute and chronic inflammatory reactions of the mesenchyme with *current terminology*; and this difficulty has arisen in connection with the term the "Reticulooses" which has appeared within the last twenty years and has never been clearly defined or accepted generally in the curriculum of the under-graduate teaching of pathology.

In order to clarify the present difficulty, and to understand what is implied if the word reticulosis is to be used at all, it is necessary to consider the history of our knowledge of cellular pathology and of the mesenchymal reactions in particular, and to accept some definitions.

The history of the working out of cellular pathology spreads over only about one hundred years, and it has been carried out by two rather different lines of workers. On the one hand by the clinicians, and on the other by those who were mainly laboratory workers, that is to say the anatomists, pathologists and physiologists. These lines have converged now, but it is interesting to review their efforts separately and we shall start with the clinicians.

The acute inflammatory reaction which leads to abscess formation has been recognised for a very long time and it has been known also for long that lymphadenopathy is not infrequently part of such a process. The enlarged gland (or bubo) was sometimes the only lesion noticed because the primary site of infection was insignificant; and all degrees of chronicity in glandular swellings were recognised. Indeed chronicity was implied in the appearance of such a term as "scrofulous diathesis" which was used to describe the patient with the thick neck of chronic cervical adenitis.

However, Hodgkin's paper in 1832<sup>5</sup> appears to have been a real landmark in the slow process of separating out the lymphadenopathies. The recognition of the clinical entity which bears his name was remarkable when looked at in its setting, because at that date the leukæmias were not recognised as entities, and the causes of syphilitic and tuberculous lymphadenopathy were unknown. He described his cases as showing "enlargement of the absorbent glands following the larger arteries" and noted that they were painless and were not softened, and that the changes within them were generalised and not localised as in tuberculosis. He held that unless the word inflammation were

to be employed in a wider and looser sense than that in general use these glands could not be called inflammatory.

The tradition of what constituted the syndrome of Hodgkin's disease was passed down carefully among clinicians in Britain, and Greenfield, who was both a clinician and a pathologist, knew its pathology well. Writing in 1878<sup>4</sup> he said that if all the lymphocytes were washed out of a gland from a case of lymphadenoma "the giant cells remain adherent to the trabeculæ": I understand that he called these cells the Hodgkin giant cells.

The leukæmias were slowly separated from one another after the middle of last century but for years controversy ranged round what constituted a leucocytosis, and what was a true leukæmia. Indeed not until after 1880 when the selective stains for blood cells were introduced did the difficulties inherent in the diagnosis of the leukæmias begin to diminish.

After 1880 the discovery of the tubercle bacillus helped to separate the tuberculous lymphadenopathies from other glandular swellings, and after 1910, when the organic arsenic compounds were introduced, the syphilitic lymphadenopathies were also cleared from the field of debate. It is difficult for the present generation of doctors to realise that at the beginning of this century syphilis was a common cause of generalised lymphadenopathy in young adults.

So within this century the diagnosis of the chronic lymphadenopathies has steadily improved, and to-day there remain a few rare mesenchymal reactions whose etiology is still obscure. They are mainly lymphadenopathies and the most important of them are Hodgkin's disease, lympho-follicular lymphadenopathy (Brill Symmer's disease), the leukæmias and the lymphosarcomas. It is over this group that the word *reticulosos* has appeared like a vague cloud.

The word is used sometimes to cover any obscure glandular swelling, and at other times to include a wide range of chronic reactions such as tuberculosis and other granulomas of known ætiology. It has become popular with radiologists because the closely packed cells of many mesenchymal hyperplasias and tumours respond to relatively small doses of radiotherapy, and are called radiosensitive.

To turn now to the history of the laboratory workers' contributions to the working out of the mesenchymal reactions. Waller,<sup>12</sup> the physiologist, was one of the first to realise that the pus corpuscles of acute inflammation came out of the blood vessels. In 1846 he described the stagnation of the corpuscles and illustrated their escape from the tortuous vessels in a beautiful pen sketch.

In 1861 Cohnheim<sup>2, 3</sup> began to publish his exhaustive essays on acute inflammation which have been the basis of the teaching on acute inflammation since his day. He made a special study of inflammations in the serous membranes and also in the a-vascular cornea, and recognised the importance of the reactions of the fixed tissue cells as well as that of the wandering cells of the circulation.

It was however, the work of Metchnikoff <sup>8</sup> rather later in the century which was the greatest contribution of pathology to medicine and to the understanding of the reactions of animal life to its environment. Starting with his wide knowledge of comparative pathology, and inspired by Darwin's work on natural selection, Pasteur's work on fermentation and Virchow's theory of cellular pathology, he showed, that throughout the animal kingdom certain reactive cells of the body are destined to contribute to a creature's response to injury and to invasion by noxious agents.

He showed that in the very lowly metazoa the reactive cells arise from the simple endoderm or intestinal tract, and like the intestinal cells have a digestive function. In higher forms of life, cells of the mesoderm are the active phagocytes. Later in phylogenesis endothelial cells of a coelomic cavity contribute to phagocytosis, and finally, with the appearance of a circulation not only local mesenchymal cells and endothelial cells but wandering blood cells are used to deal with tissue injury and with noxious agents. Metchnikoff called the wandering polymorphs microphages, and the mononuclear forms macrophages, the latter word including no doubt, what to-day we subdivide into mononuclear and endothelial cells, histiocytes or reticulum cells depending upon their site.

Metchnikoff also knew that the reacting mesodermal cells were concerned with anti-body formation.

Many workers, including Cohnheim and Metchnikoff used the method of injecting dyes into the circulation in order to study phagocytosis and towards the end of last century Ribbert <sup>10</sup> especially made exhaustive studies along this line. In general it was found that many cells of the mesenchyme react to, and absorb dye particles, but that on the whole the reaction is concentrated in the reticulum cells and sinusoidal endothelial cells of the hæmo- and lymphopoietic systems, and in the endothelial sinusoidal cells of certain parenchymatous organs such as the liver and suprarenal glands.

In 1924 Aschoff <sup>1</sup> reviewed all this past work and built up the theory that scattered throughout the body, albeit concentrated in some regions, there were cells which constituted a metabolic system and he called it the reticulo-endothelial system because the cells were mainly those found in the reticulum of glands and spleen or were the endothelial cells of capillary channels. It is in association with this idea of a reticulo-endothelial system arising from embryonic mesenchymal reticulum that the word reticulosis has emerged.

It is necessary here to say something of the origin of the word reticulum. In 1838 it meant the omentum, but *magma reticulare* was used by embryologists to describe the part of the mesoderm which condenses in a network of undifferentiated cells around the primitive gut, and from which all the vascular and lymphatic tissues are believed to arise. Later Hertwig called this layer the mesenchyme, or middle infusion, to distinguish it from the rest of the embryonic mesoderm.

Since then many workers, including Aschoff<sup>1</sup> and Maximow<sup>7</sup> have accepted the view that this undifferentiated tissue is the precursor of all the hæmo- and lymphopoietic tissues and of the fixed tissue histiocytes, and reticulum cell has been accepted to describe the large mononuclear type of cell which forms the medullary reticulum of the spleen and glands of the adult body. The word has unfortunately tended to become confused with reticul<sup>in</sup> which is a fine form of collagen. It is important to realise that a reticulum cell need not be associated with any tendency to lay down collagen, and that to name

TABLE I

*Some Diseases which have been included among the "Reticuloses."*

Glands showing simple sinus catarrh (histiocytic sinus reticulosis).	}	"Sinus reticuloses."
Tuberculosis. Sarcoidosis.		
Leprosy.		
Malaria.		
Dysfunctional conditions of storage :—		
Gaucher's disease.		
Xanthomas.		
Hæmochromatosis.		
Glands showing simple reactive follicles or Flemming's centres (histiocytic follicular reticulosis).	}	"Follicular reticuloses."
Brill Symmer's disease (lympho-follicular reticulosis).		
Hodgkin's disease (fibro-myeloid-medullary reticulosis).	}	"Medullary reticuloses."
Mycosis fungoides.		
Erythrodermia with lymphadenopathy.		
The leukæmias :—		
Myelogenous.		
Lymphatic.		
Etc.		
Conditions regarded as tumours :—		
Lymphosarcoma.		
Reticulum cell sarcoma (Ewing's Tumour, Kundrat's sarcomatosis).		
Myeloma.		
Chloroma.		

a tumour a reticulum cell sarcoma merely indicates that its cells resemble those of the primitive mesenchyme.

Letterer<sup>6</sup> used the word Reticulose first, and Reticulosis was supported by Pullinger<sup>9</sup> when she was studying the polymorphic histology of Hodgkin's disease. She thought that it might be used for a probable "group of diseases of the reticulum in which proliferation is followed by differentiation into one or several of the possible cell progeny." In 1938 Robb-Smith<sup>11</sup> used it in his classification of lymphadenopathies which was based on anatomical and cytological details.

Table I gives a list of some of the conditions which have at least been considered under the heading reticuloses. Others might, indeed

must, be added by any pathologist who includes a chronic inflammatory lesion of known etiology like tuberculosis into the list. An ordinary septic lymphadenitis ought to be included because polymorphs are just as much mesenchymal cells as lymphocytes. Enteric fever is a good example of "sinus reticulosos" and kala-azar is a perfect example of reticulo-endothelial disease, in which sinusoidal and reticulum cells become a veritable culture medium for a parasite which cannot be eliminated.

As we follow the list down the chronic inflammations run into the granulomas and we come to Hodgkin's disease (malignant granuloma) whose etiology is still obscure. Brill Symmer's disease (lymphofollicular lymphadenopathy) is a rare but somewhat similar remitting lymphadenopathy with, however, a different clinical syndrome.

The leukæmias are no doubt a dump heap of conditions, varying from acute hæmorrhagic diseases with hæmopoietic aplasia, to chronic lymphadenopathies showing some degree of leukæmia which may run a course of years.

At the bottom of the list are the mesenchymal proliferations which are apparently true tumours, that is to say growths in which destructive metastatic deposits may be found in any part of the body. The most important of these are the sarcomas which used to be called the small round cell, and the large round cell sarcomas, and which to-day are called lymphosarcoma and reticulum cell sarcoma respectively.

It is when reviewing a list such as this that we are reminded that the basic stuff of life is the endlessly reacting and regenerating mesenchyme of the animal body. It produces blood cells and destroys them and disposes of their break down products. In small capillary channels it distributes fluids, proteins and salts, adjusts  $pH$ , and deals with exogenous and endogenous noxious substances and foreign particles, and produces antibodies. Any disease which destroys this tissue or causes capillary channels to close up and fibrose must shorten life. A man is said to be as old as his arteries; it might be more exact to say that he is as old as his reacting mesenchyme, and it is interesting to remember that there is relatively little of this tissue in the central nervous system.

The mesenchyme is sensitive to many substances, to bacterial toxins, endocrine secretions, physical agents and to many chemicals. One need only consider the long lists of drugs and chemicals which have been employed in the treatment of the leukæmias to appreciate that cells of the mesenchyme can be destroyed rather easily at certain stages of their growth. It is on this account that so much interest centres round the chemotherapy of the obscure lymphadenopathies, chemotherapists hoping that from this approach some control of malignant disease may be reached. Interest also centres on the sensitivity of the mesenchymal tissues to atomic energy. It has been suggested that the allotted span of life on this planet may be related to sensitivity to cosmic radiations. We know at least that the normal

blood formation as well as pathological hyperplasias and tumours of the mesenchyme are relatively radiosensitive; probably the most radiosensitive pathological hyperplasia is the acute abscess.

CONCLUSION.—There is no doubt that the discussions which have arisen round the "Reticuloses" have been stimulating, particularly to pathologists. But it is doubtful whether any advance is made by using a new term to cover the more obscure of the mesenchymal reactions, especially as there is no indication whatever that the new name has any etiological connotation or significance. It seems that nowadays the introduction of a new word into the over-burdened descriptive vocabulary of pathology is helpful only when it contributes some advance in knowledge of the etiology of disease.

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# JUDGMENT IN CARDIOLOGY

By RICHARD W. D. TURNER

(Continued from p. 12)

## PART II

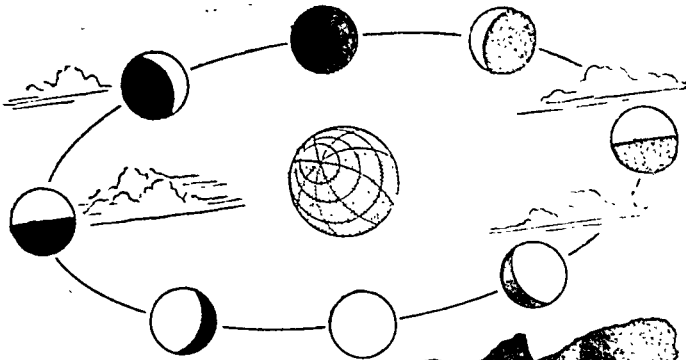
### HEART SOUNDS AND MURMURS

APART from knowledge and experience, a pre-requisite for accurate diagnosis is training in technique. By technique is meant not merely a physical process but a mental one. For example, some murmurs will be missed by failing to examine in a certain way. A mitral pre-systolic murmur, as is well known, is most likely to be heard by listening precisely at the apex with the patient lying on the left side, following exertion, and preferably perhaps, with a Bell stethoscope. An aortic diastolic murmur is best heard by listening down both sides of the sternum, with the patient standing or sitting and the breath held in expiration and preferably, perhaps, with a diaphragm chest-piece. However, just as important is the mental drill which may have to be practised for years before it becomes unconscious and automatic. This has been emphasized by Dr William Evans.<sup>2</sup> Do I hear two heart sounds and are they normal? Do I hear more than two heart sounds and if so, which is the added one. What is its quality and time relationships? A similar mental process should be applied to abnormal or added sounds: for example, an accentuated aortic second sound occurring without obvious reason should suggest listening with especial care for an aortic diastolic murmur. An added sound in early diastole should remind one that it may be followed by a distant mid-diastolic murmur. Extra sounds and murmurs may be timed through reference to the normal heart sounds which, in turn, may be recognised on auscultation, or more certainly by timing with the carotid pulse. Such details must be mastered at the bed side.

*Mitral Systolic Murmurs.*—The problem of the systolic murmur is a perennial one and many papers have been written on the subject. These remarks are confined to the problem of the systolic murmur in the mitral area as it presents in the Out-Patient Department, that is to say in those who are not ill with some acute infection.

Undoubtedly, the pendulum has swung to and fro and, rather than coming to rest midway between extremes, still oscillates over a wide arc. The unwarranted anxiety and disablement and the payment of large sums in pensions on account of innocent systolic murmurs in the first world war is well known. This was followed by a tendency, between wars, to ignore too many systolic murmurs. Now there are commendable efforts made in many quarters to assess each murmur

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critically, but the problem still exists and further pensions are being granted unnecessarily from the recent war.

The problem, then, is how to make such an assessment. First, is the murmur really present? As Levine emphasized, has it definite duration and intensity?<sup>3</sup> It is a fact that the louder or harsher the murmur, the more likely it is to be significant. An obvious exception is a ventricular septal defect in which a loud murmur may be associated with a small aperture. The position of maximal intensity should also be noted for the murmur may be transmitted; but the area over which it can be heard is naturally proportionate to its intensity. It is worth noting that aortic stenosis is sometimes the unrecognised cause of a murmur heard at the apex.

Next perhaps, is the heart enlarged? If so, the murmur must be assumed to be of organic origin. If not, then other things being equal and with certain exceptions, it can probably be ignored. Radioscopy should be part of the routine assessment because only in this way can one be certain there is no enlargement.

Is there a thrill? This seemingly elementary questionnaire is part of the essential mental discipline by which mistakes of omission can be avoided. If there is a thrill, and it must be definitely sought for, then, if maximal in the mitral area, it means mitral stenosis. Other thrills may, of course, be transmitted and be palpable, though with less intensity, at the apex; for example, from a ventricular septal defect on the left near the lower end of the sternum, from aortic stenosis in the aortic area, from pulmonary stenosis in the pulmonary area or that accompanying the Gibson murmur of patent ductus arteriosus to the left of the upper sternum; but a thrill maximal at the apex means mitral stenosis to all intents and purposes.

Next, it is best to exclude seriatim the common causes of organic systolic murmurs in the mitral area: rheumatic mitral disease; hypertension; aortic valvular disease and calcification of the valve rings. The diagnosis of these conditions will naturally be made from the physical signs and X-ray findings.

To-day in some medical circles it is hardly becoming to speak of mitral incompetence. Just as a pre-systolic or mid-diastolic murmur is accepted as evidence of mitral stenosis, so now a mitral systolic murmur, together with an enlarged left auricle on the screen, is held to have the same significance; but it is not always so. Certainly when an apical systolic murmur represents mitral disease, stenosis of the valve is usually present, but sometimes a lone mitral systolic murmur means lone mitral incompetence and the enlarged left auricle results therefrom. This may be demonstrated post-mortem, but the difficulty is that these patients do not often die, or not for some years later, when mitral stenosis may have supervened. In these cases, it may be seen on the screen that there is a systolic expansion of the left auricle, that is to say synchronous with contraction of the ventricles and it may well be that this indicates incompetence of the mitral valve.

Such apparent expansion must be distinguished from movements transmitted from ventricular contraction.

This particular problem is largely of academic interest, for it is sufficient to speak of rheumatic mitral disease which may be diagnosed on the strength of a systolic murmur and enlargement of the left auricle and to assess the disability and the outlook on other factors such as the size of the heart, evidence of impairment of myocardial function and the peripheral circulation.

A systolic murmur at the apex commonly accompanies considerable hypertension and cannot always be due to relative mitral incompetence from dilatation of the A-V ring, for it is often present long before there is any evidence of failure.

The mechanism of the apical systolic murmur usually found in cases of aortic valvular disease may also be obscure, but here too the emphasis should be on the fact that an ætiological cause for every such murmur should be diligently sought.

*Diastolic Murmurs.*—Save in some cases of anæmia and of hypertension, diastolic murmurs usually signify structural change. It is not perhaps sufficiently emphasized in clinical teaching that, quite apart from location and quality which may be misleading, the timing of diastolic murmurs helps to differentiate them. The murmur of aortic incompetence is invariably early and follows, or rather begins with the second sound (Fig. 5).

That of mitral stenosis is never early but occurs an appreciable interval after the second sound. In tachycardia, of course, this differentiation may be difficult and one must wait for the heart rate to settle from rest or treatment.

The so-called mid-diastolic murmur of mitral stenosis often starts with an added sound (or snap) which occurs an appreciable interval after the second sound. Apparent pre-systolic accentuation is dependent on auricular systole. Actually, "mid-diastolic" is not a good term because it suggests a position precisely half-way between the second and first sounds, which is not necessarily accurate. These various murmurs are, of course, often combined (Fig. 5).

The Austin Flint murmur of aortic incompetence may be indistinguishable from the diastolic murmur of mitral stenosis on auscultation. Where there is doubt, X-ray screening is invaluable and other evidence such as the state of the peripheral circulation, must be considered. Mitral stenosis usually tends to produce a small, low-volume pulse and aortic incompetence a full, bounding one.

A short, aortic diastolic murmur occurs in some 5 to 10 per cent. of cases of hypertension, with a structurally normal valve, from dynamic dilatation and is of no special moment. A similar murmur may also be found in coarctation of the aorta.

The pulmonary diastolic murmur first described by Graham Steele in cases of mitral stenosis, accompanies dilatation of the pulmonary valve or ring. It is best heard in the second right intercostal space,

usually follows an accentuated second sound and may appear superficial, as though produced just under the stethoscope. It may be confused with the murmur of aortic incompetence but there will be absence of the peripheral signs of aortic disease; screening will show enlargement of the right ventricle, rather than of the left, and dilatation of

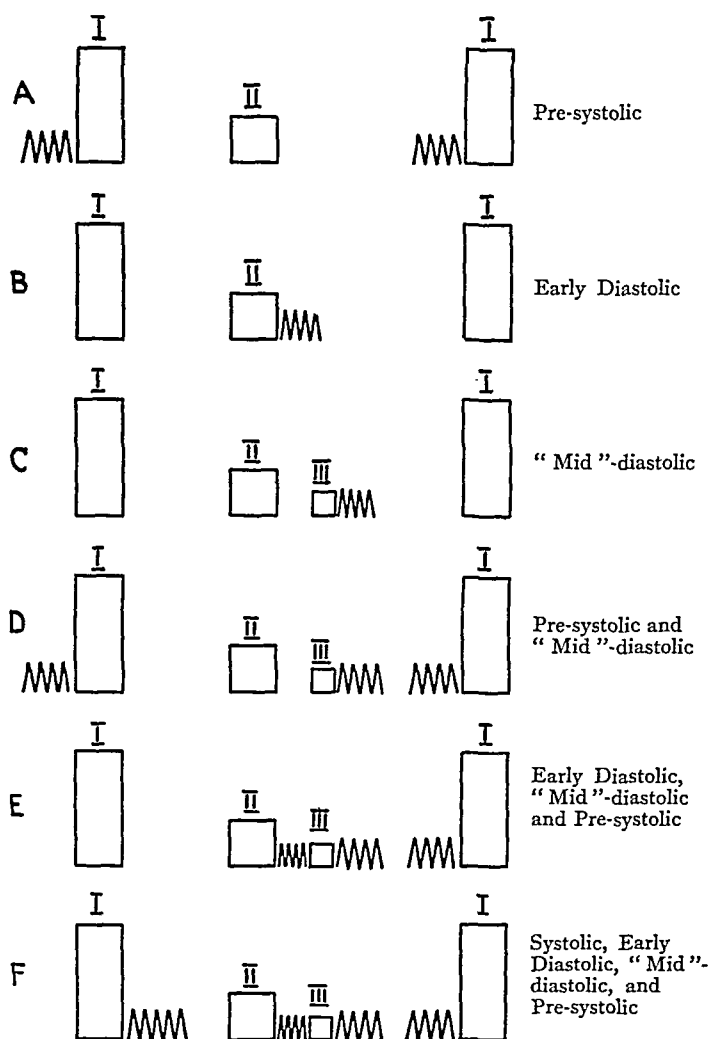


FIG. 5.—Heart murmurs.

the pulmonary artery and the E.C.G. will often show right ventricular preponderance. Pulsation of the pulmonary artery is usually also palpable. A similar murmur may, of course, accompany marked dilation of the pulmonary artery from any cause, notably in auricular septal defect. Sometimes it will first suggest the possibility of this latter condition.

*First Heart Sound.*—No certainty exists about the composition of

the first heart sound and perhaps there never will be complete agreement. This does not greatly matter. Suffice it to know that the different factors concerned are believed to include muscular, valvular and vascular components, preceded by residual auricular vibrations. Normally, these various components are heard as one by the human ear.

It will be appreciated that under certain circumstances there may be accentuation of one or the other with the production of slight impurities on auscultation. Moreover, this would be expected if the auricular component were separated as a result of delay in A. V. conduction (as reflected in prolongation of the P-R interval on the electrocardiogram). Rarely an impurity may be due to an asynchronism in the contraction of the two sides of the heart.

Timing the first heart sound with the venous pulse and the electrocardiogram has shown that it may be divided into three periods: auricular vibrations, an isometric contraction phase and an ejection

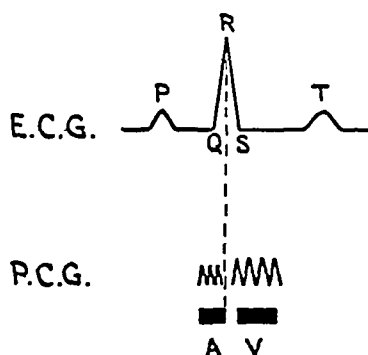


FIG. 6.—First heart sound.

E.C.G. = Electrocardiogram.

A. = Auricular component.

P.C.G. = Phonocardiogram.

V. = Ventricular component.

(These abbreviations have the same significance in subsequent figures.)

phase. For practical purposes, the E.C.G. and a sound record (phonocardiogram) may be simultaneously recorded quite easily (Fig. 6). Everything before the R. wave of the Q.R.S. complex is of non-ventricular origin. The auricular component of the first heart sound may be seen just before the R. wave. This should be distinguished from the auricular or fourth heart sound which begins on the descending limb of the P. wave and which is referred to later (Fig. 11).

Sometimes, in normal people, an apparent splitting of the first sound is heard. The term "duplication" is best avoided for, in fact, there is no duplication, as the sound record shows.

In passing, it may be pointed out that the term "re-duplication" which is in common use, literally signifies quadrupling, which is certainly not what is meant.

The split sound is best heard over the apex, or sometimes between the apex and the sternum, with the subject standing up and in expiration. Both components have much the same quality and are separated

from one another by a very short interval. The importance of the split first sound lies in its recognition. It is of no pathological significance and often accompanies the healthy heart. It may, however, be mistaken for a pre-systolic murmur, especially in an over-acting heart and a diagnosis of mitral stenosis thereby made. This, of course, is a serious error. Again, it must be distinguished from the pre-systolic sound in triple rhythm of left ventricular failure. In this latter instance, the extra sound precedes the normal first sound by a readily appreciable gap and has quite a different quality, being dull or muffled. These conditions can usually be differentiated by ear (Fig. 7).

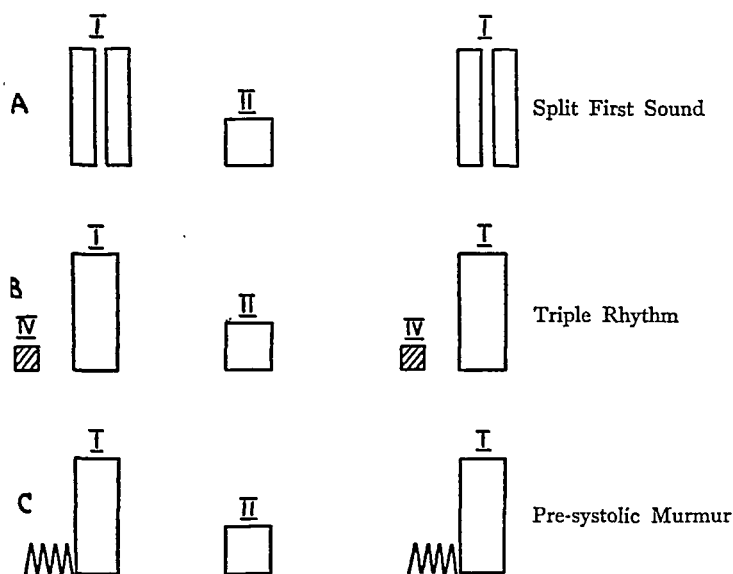


FIG. 7.—Differential diagnosis of split first sound.

Where there is uncertainty, the other evidence should be considered. Is there reason to doubt that the heart is healthy? Examine carefully for other signs of mitral stenosis. Is there present any condition that might lead to left ventricular failure or other evidence of failure in the symptoms or signs? An E.C.G. can be taken to determine the P-R interval and the presence or absence of bundle branch block. Finally, the heart may be screened for enlargement.

A simple, loud first sound may be heard in hypertension or with tachycardia for any reason, for example thyrotoxicosis; but with a normal heart rate, a sudden, sharp first sound should serve as a reminder to think of mitral stenosis and to listen carefully for a pre-systolic murmur.

*Second Heart Sound.*—There is agreement that the second heart sound is due to closure of the semi-lunar valves and concludes systole. There may be accentuation of the second sound in the aortic area in hypertension or atheroma even without hypertension, but this finding



is not constant. Accentuation often accompanies an aortic diastolic murmur and should be a reminder to listen with particular care, for such a murmur may easily be missed without special attention.

Accentuation of the pulmonary second sound usually signifies pulmonary hypertension. It is not, therefore, an early sign of mitral stenosis as sometimes taught. It is best heard at the base, in the second left intercostal space and in expiration. Splitting may accompany a loud second sound or be due to asynchronous closure of the aortic and pulmonary valves. Splitting is only of importance as regards

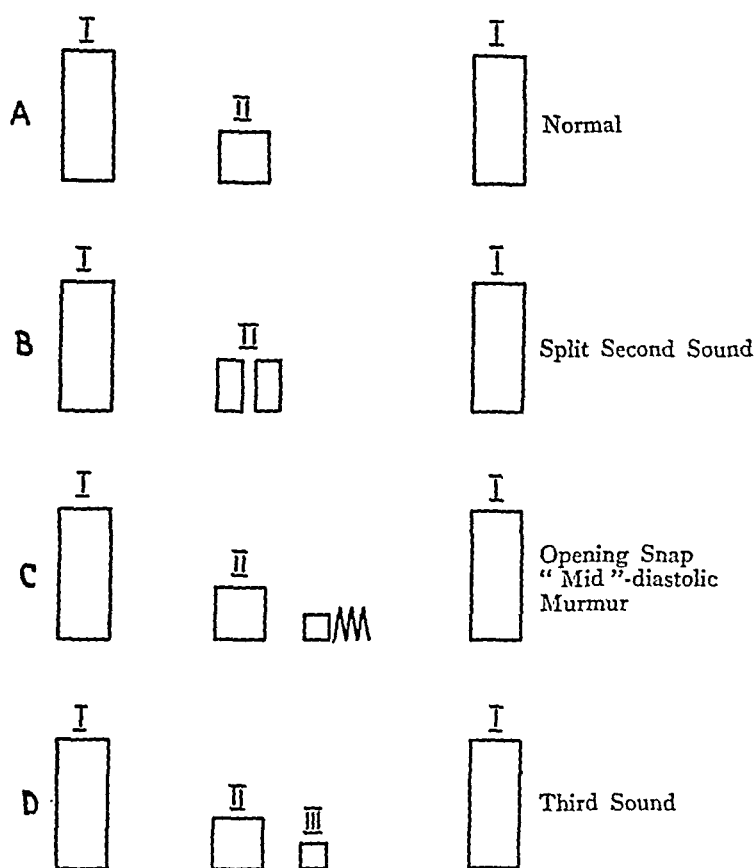


FIG. 8.—Heart sounds. Differentiation of split second sound.

differential diagnosis. This will be from the opening snap of the mitral valve and from a physiological or pathological third heart sound, which will be discussed later (Fig. 8), but it may be mentioned here that although a third heart sound can rarely by itself be distinguished from an opening snap by ear alone, either can readily be distinguished from a split second sound.

*Third Heart Sound.*—A common error in relation to the second sound is so-called re-duplication, in reality due to an audible third heart sound. This sound may usually be recorded a short interval after the second sound. Complete agreement has not been reached but probably the third heart sound is of muscular origin and produced

by vibrations of the ventricular walls, caused by the rapid inrush of blood from the auricles. Its intensity is therefore dependent partly on the degree of suddenness with which blood enters the ventricles and partly on muscular tone. The former is related to the difference in pressure between the auricles and ventricles when the valves open. The latter factor is prominent in pathological conditions.

The third sound occurs more than 1/10th of a second after the second sound. This is an appreciable interval which varies within narrow limits and is practically constant for any individual and independent of the pulse rate. The distance to the subsequent first sound varies with the duration of the cardiac cycle. The third sound always co-

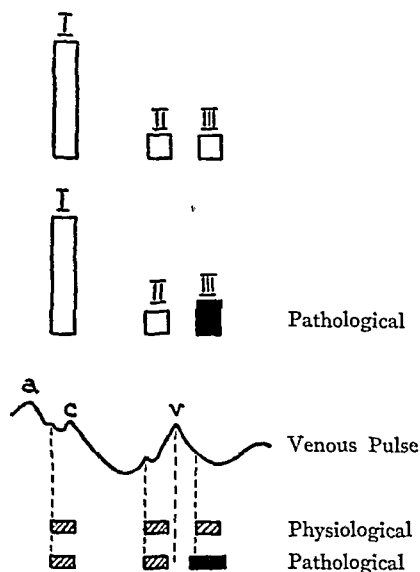


FIG. 9.—Third heart sound.

incides with the descending line of the ventricular wave of the venous pulse, that is at the end of the phase of rapid ventricular filling (Fig. 9).

This physiological third heart sound may frequently be found in healthy young people with normal hearts. It is best heard with the subject lying down and especially after exercise, which increases the venous return. Its appreciation depends on training and experience and, of course, on hearing capacity. It tends to be mistaken for the mid-diastolic murmur of mitral stenosis or for a pathological triple rhythm (Fig. 10). All observers are agreed that it is commonest in children and William Evans states that he has rarely recorded it in anyone over 30 years of age.<sup>3</sup> A girl of 17 is at present under observation for the dispelling of a cardiac neurosis, the seeds of which were sown 11 years ago and have been well watered since by a succession of school doctors. The error has lain in the failure to recognise the significance of a rather obvious third heart sound, in a perfectly normal

child. In consequence, she has not only been kept off all games but treated as a semi-invalid. It is important for all who have to make decisions as to whether a heart is healthy, to be thoroughly familiar with this sound. There should not be any difficulty in differentiating it from the pathological variety, even though the method of production is similar. In the latter instance there will invariably be other evidence of cardiac failure and the prognosis is grave, whereas by contrast the physiological sound accompanies a heart in which no other abnormality is even suspected.

*Opening snap of the Mitral Valve.*—In mitral stenosis an extra sound may often be heard early in diastole. It is of considerable value in diagnosis in calling attention to the possibility of a mid-diastolic

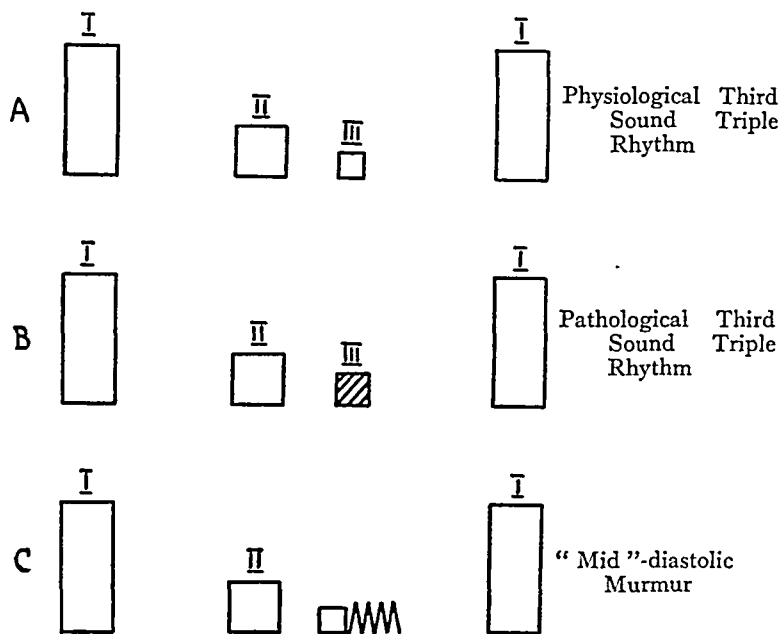


FIG. 10.—Differential diagnosis of third heart sound.

murmur being present, especially in the presence of auricular fibrillation, when the murmur may not easily be heard. It is probably produced by vibrations in the sclerotic mitral valve cusps when they open at the beginning of diastole and is characteristically a short, sharp sound, often localised to a limited area between the apex and the sternum unless very loud, when it may even be heard over the whole precordium. It occurs shortly after the second heart sound but usually somewhat earlier than the position of the third heart sound, though this difference can scarcely be appreciated by ear.

Often it seems to pass directly over into the mid-diastolic murmur (Fig. 10). The silent gap after the second sound is valuable in the differentiation from the early diastolic murmur of aortic incompetence which immediately follows the second sound. This sound was first described in 1888 by Rouches,<sup>8</sup> a pupil of Potain,<sup>7</sup> who called it "le claquement d'ouverture de la mitrale," and was later termed the

"opening snap of the mitral valve" by Thayer in 1909.<sup>9</sup> As mentioned above, it should be differentiated from a split second sound or a third heart sound (Fig. 8). "Snap" is now in common usage but is not really a good descriptive term because it is difficult to picture thickened cusps snapping open, though easy to imagine them causing loud vibrations. An appreciation of this opening sound materially assists in timing and recognising a mid-diastolic murmur and commands attention to this point. Once the conditioned reflex of listening is established, it will be heard and recognised more frequently and its significance appreciated and in time, it will not be mistaken for other sounds. It may be heard more often than not in cases of mitral stenosis, whether there be normal rhythm or auricular fibrillation.

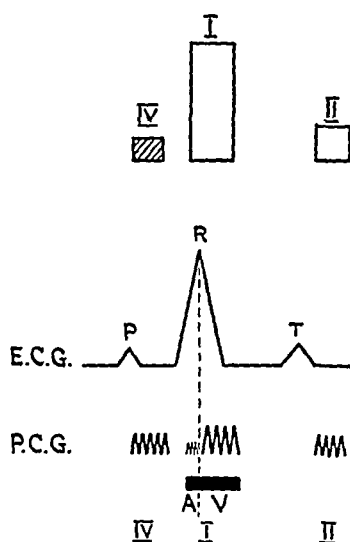


FIG. 11.—Fourth heart sound.

*Fourth Heart Sound.*—It has been established by phonocardiography that a fourth heart sound can be registered late in diastole in normal people. This physiological sound is dependent on auricular systole and will therefore disappear with the onset of auricular fibrillation. It is faint, of low frequency, and occurs immediately before the strong first heart sound. For these reasons, it is usually barely audible. However, it may often be heard in complete heart block. There are probably three components dependent on actual contraction of the auricle, ventricular vibrations from the inrush of blood and closure of the A.V. valves. Simultaneous electrocardiographic and phonocardiographic tracings show that it starts immediately after the P. wave of the electrocardiogram (Fig. 11). In normal people, a sound in this position can be constantly recorded via the oesophagus and investigations indicate that this component originates from actual auricular contraction. The sound in this position which can often be recorded

over the chest wall, is probably due to the ventricular and valvular components.

Normally, this fourth heart sound cannot be heard on auscultation so that when it is heard, an explanation must be sought. We have seen that the normal first heart sound includes residual vibrations dependent on auricular contraction and a split first sound may sometimes be due to separation of this component. When the fourth heart sound is heard, it can usually be recognised as distinctly separate from the first sound and of a different quality. This fourth sound may be heard in cases where there is delay in A.V. conduction but it is not always audible in such instances. By far, the commonest clinical association is left ventricular failure with normal rhythm, that is to say, the familiar classical "bruit de galop," the two factors responsible being auricular contraction and the dilated atonic ventricle.

Admittedly, there is no *a priori* reason why there should not sometimes be heard every gradation of sounds between a split first sound and a very distinct and well-separated gallop rhythm. Fortunately, in practice, there is seldom difficulty in distinguishing between them but there will always be room for differences of opinion and other human factors and so the phonocardiogram should be as readily available as the electrocardiogram.

*Triple Rhythm.*—Triple rhythm is a reasonable term to use whenever three sounds can be heard instead of the normal two. Since this expression covers both the physiological and pathological forms, it will require further description in any given case, for example, triple rhythm due to the physiological third heart sound or to the added sound which often precedes the mid-diastolic murmur of mitral stenosis; or triple rhythm due to the pathological fourth sound of left ventricular failure. The meaning of triple rhythm should always be sought because it will give additional and useful information about the patient. Some physicians place great reliance on these extra sounds and others almost ignore them. It may be contended that this is a sport for cardiologists of academic interest rather than practical importance. Even then, the pursuit of knowledge would be justifiable for its own sake, though admittedly more stimulating if there be some practical application in view. However, I believe they are of definite value as an associated factor in the assessment of the case if taken in conjunction with other findings. Seldom are they significant as a single sign.

Just as important are the errors of judgment based on misinterpretation. The problem is complex in that it is difficult to establish the precise mechanism of production, but on the whole there is close agreement amongst cardiologists on their clinical significance. Unfortunately, the nomenclature used by different teachers and textbooks is most confused and this adds greatly to the difficulties of the student.

*Gallop Rhythm.*—Gallop rhythm is the term traditionally applied

to triple rhythm associated with cardiac failure and carries a serious prognosis.

There is a systolic form which is rare and of unknown origin but which has no pathological significance. It occurs during systole just before the second sound and the only importance of this extra sound lies in differentiating it from diastolic gallop rhythm. This can usually be done clinically.

Although phonocardiography has done much to clarify clinical interpretation and can therefore largely be dispensed with as a routine, always there will be room for doubt from the human factor and from genuine differences of opinion. This is one good reason why it should be as readily available as is the electrocardiogram for arrhythmias. Modern methods of phonocardiography may be expected to help in the solution of remaining problems. One of the difficulties has been the lack of agreed technical standards and, in particular, the employment of different frequency ranges by various workers. In Sweden, Mannheimer has been working with a calibrated phonocardiograph over the whole range of frequencies and such a machine must be of great assistance in research work.<sup>4</sup> In the past, the only differentiation between physiological and pathological sounds has been from the presence of other signs of cardiac disease. Mannheimer claims to have shown that the gallop sound has a higher frequency and a higher amplitude than the corresponding normal sounds, so that there may now be an objective definition of gallop rhythm.

Potain<sup>7</sup> was the first to divide pathological diastolic triple rhythm into two groups, both dependent on decreased ventricular tone, one occurring early and the other late in diastole. He introduced the terms proto-diastolic and pre-systolic gallop rhythm. The former is a bad term in that proto-diastolic is used by the physiologists with reference to the period just before the opening of the semi-lunar valves. He also distinguished between left and right-sided forms, according to whether the gallop is presumed to occur in the left or right side of the heart, the former being best heard at the apex and the latter near the xiphoid.

The modern tendency is to abandon the older terms and refer to third sound or rapid filling gallop and fourth sound or auricular systolic gallop. These sounds are identical in most respects with the physiological third and fourth sounds and are but an accentuation of them (Fig. 12).

Diastolic gallop rhythm may accompany failure of either ventricle or failure of both ventricles together. When some condition involving left ventricular strain is present, such as hypertension, aortic valvular disease or coronary atheroma, it is usually best heard over the apex and then occurs late in diastole because it is dependent on auricular systole; the other factor being the decreased tone of the failing left ventricle. Obviously it will disappear should auricular fibrillation supervene.

When some condition involving right ventricular strain is present, such as previous left ventricular failure, cor pulmonale or congenital heart disease, the added sound is usually best heard nearer the sternum and occurs early in diastole because it is dependent on rapid auricular filling, secondary to increased pressure in the great veins; the other factor being the decreased tone of the failing right ventricle. It will not be influenced by auricular fibrillation.

When the ventricles fail together, as often happens, there is usually tachycardia and, whenever there is tachycardia, the cardiac cycle may

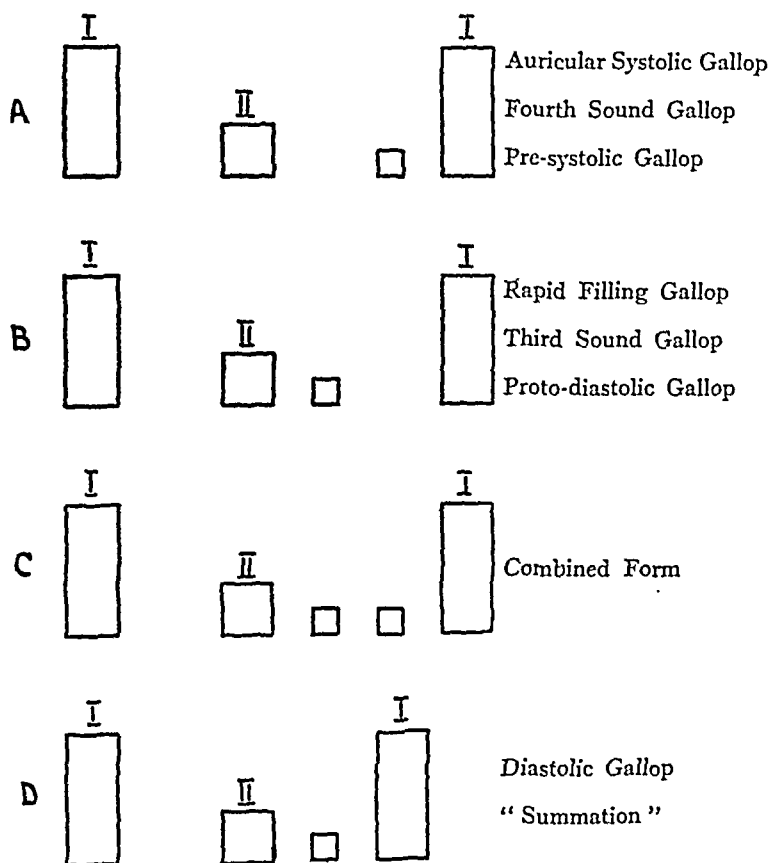


FIG. 12.—Gallop rhythm.

be so shortened that precise timing is impossible and one can but refer to diastolic gallop rhythm. The term "summation gallop" is not a good one in that it suggests that both gallop sounds are present together, which may or may not be the case. When the pulse rate slows, they may be heard separately as a quadruple rhythm from addition of the third and fourth sounds. It can then be appreciated that there had, in fact, been present summation gallop. At other times, it will be found that with slowing of the heart, the extra sound appears early or late in diastole (Fig. 12).

Gallop rhythm is a grave sign occurring in conditions in which cardiac failure may be expected. If heard unexpectedly, then either other abnormal signs will be present or there has been an error in

interpretation and the answer will probably be found on reconsideration of the evidence.

Now and then its definition will first suggest a correct diagnosis. This is especially liable to be the case when left ventricular failure has been mistaken for some pulmonary disease such as pneumonia. A good example which occurred during the war was that of a senior officer who was said to making rather a slow convalescence from pneumonia. The discovery of pre-systolic triple rhythm led to the taking of an electrocardiogram, which showed the existence of a recent myocardial infarction. He died a few weeks later.

Two other recent examples of the importance of taking the whole case into review may be quoted :

A woman of 25 years was referred from the ante-natal clinic on account of triple rhythm with tachycardia. It was found that the

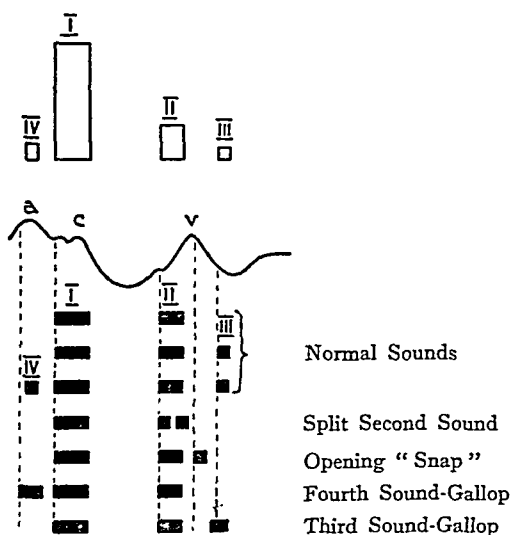


FIG. 13.—Composite diagram to show the approximate position of the various heart sounds in the cardiac cycle as shown by simultaneous recordings of the venous pulse with the phonocardiogram.

hæmoglobin was 40 per cent. and the triple rhythm could be explained by rapid ventricular filling due to the increased minute volume and rate of blood flow associated with anæmia. It disappeared completely with the cure of anæmia. No other abnormality in the heart was found.

A girl of 19 with Friedreich's Ataxia was found, on routine examination to have the characteristic electrocardiographic changes associated with this condition but no clinical abnormality in the heart or evidence of failure. Shortly afterwards, however, she developed œdema of the legs, filling of the neck veins and the triple rhythm characteristic of right ventricular failure. The poor prognosis associated with this form of gallop was justified by subsequent events in that she died within a few weeks.



*Bundle Branch Block.*—Various forms of triple rhythm may be heard in bundle branch block and this has given rise to much confusion and disagreement. Obviously, since it is often associated with serious coronary disease, there may be present triple rhythm from left ventricular failure and, since latent heart block with a prolonged P-R interval is another common association, triple rhythm may be present from this cause. Some consider that gallop rhythm in bundle branch block is always due to such causes but there is little doubt that it may be heard in the presence of auricular fibrillation and with a normal P-R interval and persist if the auricular fibrillation is replaced by a normal rhythm and that, in such cases, there is no apparent change in the timing or quality of the extra sound. A case was published some years ago when triple rhythm disappeared, with a coincident disappearance of bundle branch block, as proved on the electrocardiogram.<sup>1</sup>

From these reasons we must accept a form of triple rhythm dependent on bundle branch block alone and presumably due to asynchronous contraction of the two ventricles.

In summary, then, triple rhythm must first be differentiated from splitting of the first or second heart sounds. An extra sound occurring shortly after the normal second heart sound, may accompany either the healthy heart of young persons or a failing right ventricle and should always serve as a reminder to examine carefully for the diastolic murmur of mitral stenosis. An extra sound occurring shortly before the normal first heart sound usually means left ventricular failure (Fig. 13). If an electrocardiogram shows the absence of bundle branch block and of prolongation of the P-R interval, then other evidence of left ventricular failure should be sought and also the ætiological cause for such failure.

Triple rhythm is a common source of difficulty and this classification should not be considered absolute or final but it has at least the merit that few cases in practice fail to fit in and find satisfactory explanation. This is not to deny, however, that there remains a small group of mystery cases which can only be reduced by adequate follow-up and pathological study.

As in the hey-day of percussion, it was easy to percuss pre-conceived ideas into the cardiac outline, so to-day there may develop a tendency to identify an added sound in a similar way, but with increasing experience and a critical, even sceptical outlook, errors will be few and rarely important. Agreement on these problems should be possible; until such is reached, students must be excused confusion.

A wide variety of diverse and apparently unrelated aspects in cardiology have been touched on in this paper. Perhaps a central theme may be detected in the stress laid on the value and importance of meticulous assessment of each patient in order to avoid errors of judgment that so often lead to quite unwarranted restrictions.

The figures in this paper have been made as simple as possible to try and make the explanation in the text clear. They are not accurate representations of the exact timing of events in the cardiac cycle.

## ACKNOWLEDGMENTS

It is not possible to acknowledge the sources from which many of these remarks must subconsciously have been drawn. My gratitude is chiefly due to Sir John Parkinson, Dr Evan Bedford and Dr William Evans of the National Hospital for Diseases of the Heart in London.

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## NEW BOOKS

*Progress in Clinical Medicine.* Edited by RAYMOND DALEY, M.A., M.D., M.R.C.P., and HENRY G. MILLER, M.D., M.R.C.P., D.P.M. Pp. xi+356. London: J. & A. Churchill Ltd. 1948. Price 21s.

Twelve distinguished contributors have undertaken to review and present the latest views in different departments of medicine. Each chapter contains the latest information on a number of disorders so that the book as a whole gives an excellent account of all the most recent advances in practical medicine. Dr Henry G. Miller who deals with diseases of the nervous system also contributes a chapter on psychosomatic medicine. This concept he admits represents a phase in the integration of psychiatry into the fabric of general medicine, but eventually the term must become superfluous when all medicine has become psychosomatic.

The book can be thoroughly recommended to all who pride themselves in keeping abreast with modern progress.

*The Nursing of Tuberculosis.* By O. V. BUXTON, S.R.N., and P. M. MACKAY, S.R.M.N. Pp. 124, with 23 figures. Bristol: John Wright & Sons Ltd. 1947. Price 7s. 6d.

The authors have written this little book in order to enable nurses to give the tuberculous patient all the care that is necessary to promote recovery and to maintain the "chronic" case in as comfortable a state as possible.

Anatomy, pathology and bacteriology are touched on in the first four chapters. The rest of the book deals with matters of more importance to the nurse. The book is well written and should be of the greatest assistance to those who are engaged in this type of nursing.

*The Appendix.* By R. J. MCNEILL LOVE, M.S. (LOND.), F.R.C.S. (ENG.). Pp. vi+188, with 54 illustrations. London: H. K. Lewis & Co. Ltd. 1947. Price 12s. 6d. net.

This manual has been written as a guide for younger surgeons who are responsible for much of the emergency work in hospitals. All sorts and conditions of the appendix, all methods of treatment, and numerous complications are dealt with. It contains many excellent illustrations and presents the subject well. However, it is rather a lengthy book due mainly to the inclusion of countless personal experiences of the author. These stories, and the simple way in which it is written, make very easy and interesting reading.

*Clinical Methods in Surgery.* By K. DAS, M.B. (CAL.), F.R.C.S. (ENG. AND EDIN.). Pp. 240, with 199 illustrations. Calcutta: The City Book Company. 1947. Price 35s.

This book is designed to show the student how to carry out a systematic clinical examination of the various parts of the body. It denotes separate chapters to surgical case-taking, and the examination of a tumour, an ulcer, head injuries, fractures, and so on. The book is full of good illustrations and they form the best feature. The text tends to be dull as it consists only of numbered lists of questions to be asked and tests to be carried out in the examination. But it is not easy to demonstrate clinical methods in a book, and the author has succeeded well.

*Tuberculosis in the Commonwealth 1947.* Complete Transactions of the Commonwealth and Empire Health and Tuberculous Conference. London: N.A.P.T. Price 15s. net.

This conference was held in London from 8th July to 13th July 1947 and was attended by speakers from the whole Empire. The discussions covered a wide

variety of subjects:—Tuberculosis in the Commonwealth: The National Health Service Act and Its Effect on Tuberculosis Work: Sanatorium Design: Care and Rehabilitation Schemes: Specific Measures for the Prevention and Treatment of Tuberculosis including Streptomycin and B.C.G.: Propaganda, Psychology, and Education: and the Colonial Tuberculosis Services. The papers and discussions are given in full and the publication is a permanent record of a conference which produced much that was of interest and permanent value.

*The Preparation of Solutions Iso-osmotic with Blood, Tears and Tissue.* By C. G. LUND, E. P. NIELSEN and K. PETERSEN-BJERGAARD. Pp. 173, with 40 figures and 146 tables. London: William Heinemann (Medical Books) Ltd. 1947. Price 15s. net.

This useful book has been compiled at the request of the Danish Pharmacopœia Commission, and contains a great mass of information on the preparation of iso-osmotic solutions of substances in general medical use, and especially in ophthalmology. Determinations have been made by lowering of the vapour pressure and by depression of the freezing-point, and the whole text has the air of a very accurate compilation of scientific data. It should be of extensive use to many investigators outside the field of pharmacy, and may well become a standard reference book in this interesting branch of physical chemistry. The Danish text has been translated by Hans Tang.

*The Beginnings of Modern Medicine in Madras.* By Professor D. V. SUBBA REDDY. Pp. x+244. Calcutta: Thacker, Spink & Co. 1947. Price 5 rupees.

Professor Reddy makes an important contribution to the history of the introduction of western medicine into India based on the development of the Madras General Hospital and Medical College from small beginnings. The material is clearly the result of exhaustive research and study of original records. Extracts from records dating from the time of the settlement of the East India Company throw a light on the somewhat elementary and inadequate medical arrangements supplied by the Company for its officers. The gradual awakening to necessities and the extension of medical aid to the indigenous population form part of the story. Interesting glimpses are given of the character and experiences of some of the earlier surgeons. It appears that their experiences were as varied as their characters. Professor Reddy is to be congratulated on having collected and selected so much of interest from numerous published and unpublished sources which might otherwise have passed into oblivion.

*The Metabolic Brain Diseases and Their Treatment.* By G. TAYLEUR STOCKINGS, M.B., B.S., D.P.M. Pp. vii+262, with 3 illustrations. London: Baillière, Tindall & Cox. 1947. Price 16s. net.

In this book an admirable attempt is made to describe the different mental states for which "shock" therapy is advocated and as well as to discuss the physiological and chemical mechanisms governing this method of treatment. Many of the answers are of necessity as yet incomplete or *sub judice*, but no matter, the assessment given at this stage is well worth while, revealing as it does a notable awareness of the vast amount of literature which has so rapidly grown up around the subject. Some of these reveal an American school of thought concerning psychophysiology, which in this country we have perhaps paid too little heed.

An important chapter is devoted to the differential diagnosis from organic conditions and another shows the separation of neurotic and psychopathic states, but to distinguish between the relative worth of the fifteen chapters is unwise since each has obviously an important place in the composite picture, all are needed and the whole makes an intriguing story.

It is interesting to reflect that the metabolic brain diseases are regarded as organic conditions since in this thought alone the clinician will detect a definite step forward. The author's use of the phrase acute emotional upset (A.E.U.) is another indication of the clear and realistic presentation which characterises this useful book.

## NEW EDITIONS

*Neuropsychiatry for Nurses.* By IRVING J. SANDS, M.D. Fifth Edition. Pp. 397. London: W. B. Saunders Company. 1948. Price 15s. net.

This well-known book for nurses has stood the test of time. The chapters dealing with neuro-anatomy and with medical psychology are excellent. The description of the various clinical entities is concise and adequate, and much useful information regarding the practical care of patients is incorporated. The strong emphasis on the psychoanalytic approach, both on the part of doctor and nurse, is an indication of the trend of American psychiatry to-day. It goes a good deal further than the majority of psychiatrists in this country would consider advisable.

*Clinical Electrocardiography.* By D. SCHERF and L. J. BOYD. Third Edition. Pp. 435, with 264 figures. London: William Heinemann. 1948. Price 30s. net.

This valuable book is not only suitable for the guidance of the general physician, but it also contains much that will interest the expert. The third edition has been brought up to date and gives extended information on the use of chest leads. Reference is made in the text to some matters of clinical interest and to points about therapy. The bibliography is fairly comprehensive and the figures are satisfactory.

Electrocardiography is a complicated subject and this book should be of assistance to those who desire to keep up to date.

*Infra-red Irradiation.* By WILLIAM BEAUMONT, M.R.C.S. (ENG.), L.R.C.P. (LOND.). Third Edition. Pp. xii+162, with 32 illustrations. London: H. K. Lewis & Co. Ltd. 1948. Price 8s. 6d. net.

In a review of an earlier edition it was pointed out that the author was in error in stating that the beneficial effects of Finsen's treatment of lupus was due to the infra-red rays. The author persists in this mis-statement. He also states that the red rays are the shorter visible and that the pigmentation produced on the legs by habitually sitting in front of a fire is due to melanin. Both of these statements are incorrect. Such errors about things which are easy of proof make one doubt the value of any statement in the book, except that, as everyone knows, heat relieves pain.

*A Short Practice of Surgery.* By HAMILTON BAILEY, F.R.C.S., and R. J. MCNEILL LOVE, M.S. (LOND.), F.R.C.S. Eighth Edition in 5 parts. Part I, pp. x+232, with 259 illustrations (89 coloured). London: H. K. Lewis & Co. Ltd. 1948. Price £2, 12s. 6d. the set.

This is the eighth edition of this book to be produced in sixteen years. This edition is being published in five separate parts and must be bought complete. Thus it is hoped to overcome time lag at the publishers and so keep the ensuing parts up to date. The chapter headings and general lay out of the book have remained essentially the same. Many chapters have been re-written. The illustrations—at least one on every page—are even better and more numerous than before. Their colours adorn each chapter and make this a student's textbook of the excellence which we now expect from these authors.

*Textbook of Pharmacology and Therapeutics.* By H. N. WRIGHT and M. MONTAG. Fourth Edition. Pp. xiii+720, with 95 illustrations. London: W. B. Saunders Company. 1948. Price 20s.

To quote the preface this is "a volume of a very high standard of typographical excellence." But the text is unbalanced; fifty pages are devoted to simple arithmetic, ten lines to liver in Addisonian anæmia and seven lines to a description of Haverhill fever! Penicillin is evidently a single substance while psittacosis and ornithosis are two diseases (p. 545). The terms throughout are those of the U.S. Pharmacopœia. This book will not meet the requirements of the British student.

*A Pocket Medicine.* By G. E. BEAUMONT, M.A., D.M. (OXON.), F.R.C.P., D.P.H. (LOND.). Second Edition. Pp. viii+208. London: J. & A. Churchill Ltd. 1948. Price 9s. net.

This handy little book has already been reprinted twice since it was published in 1942. The new edition gives a clinical picture of various medical conditions and incorporates recent advances in therapeutics. It will be of great value to the student revising for "Finals," and to the newly qualified practitioner.

*Treatment in General Practice.* By HARRY BECKMAN, M.D. Sixth Edition. Pp. 1129. London: W. B. Saunders Company. 1948. Price 57s. 6d.

The fast changing therapeutic scene brings forward another edition of Professor Beckman's book after an interval of just over two years.

The plan of the book is good and achieves a sense of completeness. Each condition is first adequately summarised, important historical data included and the treatment then discussed. Comprehensive and up-to-date treatment is clearly set out. Therapeutic dead wood has been cut, though the author admits occasions on which his courage has failed. Where final decision regarding a remedy has not been reached the present position is well stated. A useful section on the treatment of allergic conditions is included. There is, too, a short chapter on geriatrics and Professor Beckman is refreshingly dubious about its necessity.

This is a well-planned book with sound material presented in a manner which is both stimulating and attractive.

*Treatment by Manipulation in General and Consulting Practice.* By A. G. TIMBRELL-FISHER, M.C., F.R.C.S. (ENG.). Fifth Edition. Pp. ix+275, with 126 illustrations. London: H. K. Lewis & Co. Ltd. Price 25s. net.

Mr Timbrell-Fisher's monograph has done much to establish manipulative treatment as a sound scientific procedure. The appearance of a fifth edition in enlarged form with many new illustrations is proof of its popularity.

An interesting historical survey of the changing attitude towards damaged joints leads to a presentation of the pathology of adhesion formation and to a discussion of the present-day views regarding prevention. Treatment of established adhesions and contractures and other amenable conditions is described on a regional basis without alarming over enthusiasm, and with adequate warning of the contra-indications. The limbs are dealt with, on the whole, clearly, but the section on the spine leaves the reader rather vague regarding the precise indications for manipulation. The illustrations manage to convey the impression of actual movement surprisingly well—a difficult feat.

The book is of great value to all those concerned with the treatment of trauma and the rheumatic states.

*The Stuff we're made of.* By W. O. KERMACK and P. EGGLETON. Second Edition. Pp. viii+365, with 8 plates and 74 figures. London: Edward Arnold & Co. 1948. Price 10s. 6d. net.

The second edition of this popular book has appeared after an interval of ten years. It continues to give a simple and straightforward account of the properties of living tissues. The subject matter covers atomic and molecular structure, enzymes, vitamins and hormones, and special attention is devoted to such biological mechanisms as growth and reproduction, muscle contraction and energy production. The whole work is well illustrated by graphs, figures and plates.

A book of this merit is bound to stimulate the imagination of the younger generation of chemists and clinicians and bring them to realise the importance of the modern advances in biochemistry. It is an excellent introduction to those starting on a career of science or medicine, and many of their elders could also read it with advantage.

# BOOKS RECEIVED

- Edited by ANDERSON, W. A. D., M.A., M.D., F.A.C.P. Pathology.  
(*Henry Kimpton, London*) 75s. net.
- BOOKMILLER, MAE M., R.N., and BOWEN, GEORGE LOVERIDGE, A.B., M.D.  
Textbook of Obstetrics and Obstetric Nursing. (*W. B. Saunders Company, London*) 22s. 6d.
- BRADLEY, DAVID. No Place to Hide (*Hodder & Stoughton Ltd., London*) 7s. 6d.
- BRECKENRIDGE, MARIAN E., M.S., and VINCENT, E. LEE, PH.D. Child Development: Physical and Psychological Growth Through the School Years. Second Edition, Illustrated (*W. B. Saunders Company, London*) 20s.
- British Medical Association. Proceedings of the Annual Meeting 1948.  
(*Butterworth & Co. (Publishers) Ltd., London*) 35s. net.
- Edited by CONN, HOWARD F., M.D. Current Therapy 1949.  
(*W. B. Saunders Company, London*) 50s.
- DEGOWIN, ELMER L., M.D., HARDIN, ROBERT C., M.D., and ALSEVER, JOHN B., M.D. Blood Transfusion . . . (*W. B. Saunders Company, London*) 45s.
- Revised by DOUTHWAITE, A. H., M.D., F.R.C.P. Hale-White's Materia Medica. Twenty-Eighth Edition (*J. & A. Churchill Ltd., London*) 16s. net.
- FELDMAN, MAURICE, M.D. Clinical Roentgenology of the Digestive Tract. Third Edition . . . (*Bailliere, Tindall & Cox, London*) 44s. net.
- FLACK, I. HARVEY, M.D. Lawson Tait, 1845-1899.  
(*William Heinemann (Medical Books) Ltd., London*) 17s. 6d. net.
- FRIED, B. M., M.D. Bronchiogenic Carcinoma and Adenoma.  
(*Bailliere, Tindall & Cox, London*) 33s. net.
- GECKELER, EDWIN O., M.D. Fractures and Dislocations for Practitioners. Fourth Edition . . . (*Bailliere, Tindall & Cox, London*) 27s. 6d. net.
- GECKELER, EDWIN O., M.D. Plaster of Paris Technic. Second Edition.  
(*Bailliere, Tindall & Cox, London*) 16s. 6d. net.
- HUNTER, GEORGE W., III, PH.D., and HUNTER, F. R., PH.D. College Zoology.  
(*W. B. Saunders Company, London*) 27s. 6d.
- INGRAM, MADELENE ELLIOTT, R.N. Principles of Psychiatric Nursing. Third Edition . . . (*W. B. Saunders Company, London*) 19s.
- JOHNSTONE, R. W., C.B.E., M.A., M.D., F.R.C.S.E., M.R.C.P.E., F.R.C.O.G., F.R.S.E. The Midwife's Text-Book. Fourth Edition (*A. & C. Black Ltd., London*) 20s. net.
- KEMP, W. N., M.D., C.M. Elementary Anaesthesia.  
(*Bailliere, Tindall & Cox, London*) 27s. 6d. net.
- LEE, MABEL, B.S., LL.D., and WAGNER, MIRIAM M., B.A., M.A. Fundamentals of Body Mechanics and Conditioning (*W. B. Saunders Company, London*) 22s. 6d.
- LEWIS, SIR THOMAS, C.B.E., F.R.S., M.D., D.S.C., LL.D., F.R.C.P. Electrocardiography and Clinical Disorders of the Heart Beat.  
(*Shaw & Sons Ltd., London*) 25s. net.
- LONGMORE, T. A., HON. F.S.R. Medical Photography. Fourth Edition.  
(*The Focal Press, London*) 50s. net.
- MAISIN, Docteur J. Cancer, Tome II. Radiations, Virus, Environment.  
(*Casterman Tournai-Paris*) —
- MELENEY, FRANK LAMONT, M.D., F.A.C.S. Clinical Aspects and Treatment of Surgical Infections . . . (*W. B. Saunders Company, London*) 60s.
- Edited by OGILVIE, SIR HENEAGE, K.B.E., D.M., M.CH., F.R.C.S., and THOMSON, WILLIAM A. R., M.D. The Practitioner Handbooks. Early Recognition of Disease . . . (*Eyre & Spottiswoode (Publishers) Ltd., London*) 10s. 6d. net.
- PARTIPILO, A. V., M.D., F.A.C.S. Surgical Technique. Fourth Edition.  
(*Henry Kimpton, London*) 75s. net.
- Edited by PATERSON, DONALD, M.D.(EDIN.), F.R.C.P., and MONCRIEFF, ALAN, M.D.(LOND.), F.R.C.P. Diseases of Children, Volume II. Fourth Edition.  
(*Edward Arnold & Co., London*) 40s. net.
- Edited by PELTON, WALTER J., B.S., D.D.S., M.S.P.H., and WISAN, JACOB M., D.D.S., M.S.P.H. Dentistry in Public Health.  
(*W. B. Saunders Company, London*) 27s. 6d.
- QUIRING, DANIEL P., PH.D. Collateral Circulation (*Henry Kimpton, London*) 25s. net.
- Edited by REES, J. R., M.D. Modern Practice in Psychological Medicine 1949.  
(*Butterworth & Co. (Publishers) Ltd., London*) 50s. net.
- SCHOENEWALD, F. S., M.D.BERLIN. German-English Medical Dictionary.  
(*H. K. Lewis & Co. Ltd., London*) 27s. 6d. net.
- The Committee on Dietetics of the Mayo Clinic. Mayo Clinic Diet Manual.  
(*W. B. Saunders Company, London*) 20s.
- WIPRUD, THEODORE. The Business Side of Medical Practice. Second Edition, Illustrated . . . (*W. B. Saunders Company, London*) 17s. 6d.

The Transactions of the  
Medico - Chirurgical Society  
of Edinburgh

SESSION CXXVIII.—1948-1949



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# The Transactions of the Medico-Chirurgical Society of Edinburgh

## STREPTOMYCIN TREATMENT OF MENINGEAL, MILIARY AND PULMONARY TUBERCULOSIS

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### INTRODUCTION

STREPTOMYCIN has now been widely used in America for some years, and in this country it is gaining increasing prominence. The already voluminous literature concerning it includes several reports embodying large series of cases,<sup>1-4</sup> and it is to such reports that we must turn for authoritative opinions. Nevertheless, as a consequence of the foundation of knowledge provided by others, it is possible to extract something of value from a study of small groups of cases. It is on these grounds that this paper may have some justification.

At Bangour Hospital 39 patients suffering from tuberculosis had been admitted for streptomycin treatment before 30th September 1948 and these form the material for this paper.

### MENINGEAL TUBERCULOSIS

Twenty-seven cases suffered from meningeal tuberculosis at the time of their admission and the results of treatment assessed on 31st October are shown in Table I. As one would expect, with prolongation of the observation period the mortality rate has increased.

TABLE I

*Cases Suffering from Tuberculous Meningitis when Admitted*

Minimum Observation Period.	Dead.	Stationary Relapse or Deteriorating.	Doing Well.	Total Cases.
31 days . .	15	2	10	27
125 days . .	10	1	4	15
245 days . .	7	1	2	10

Some of the main features of the individual cases are summarised in Table II.

TABLE  
Cases with Meningitis

Case No.	Sex.	Age.	Duration of Meningeal Symptoms in Days.	Stage.	C.S.F. Culture.	Other Positive Cultures.	Chest X-ray.	Other Lesions.	Observation Period.	Result.	Remarks.
1	F.	20	11	M.	+	Sputum	Infiltration left lung	Discharging neck gland	77	D.	Initial improvement followed by relapse with development of spinal block. Adhesions freed by operation but death a few days later.
2	F.	2 $\frac{1}{2}$	14	M.	+	...	Calcified primary complex	...	256	D.	Good initial response. Relapse at 5 months followed by further response to treatment but death following development of hydrocephalus.
3	M.	15	12	M.	+	...	Bilateral upper zone foci	...	389	D.W.	Mentioned in text. Has had spinal block since 3 weeks after admission
4	F.	13	?	E.	+	G.W.O.	Miliary	Choroidal tubercles	95	D.	Good initial response followed by relapse. Healing of miliary lesions and choroidal tubercles.
5	M.	4	21	A.	+	G.W.O.	Miliary	...	10	D.	Spinal block on admission. No response to intraventricular streptomycin.
6	M.	16	5	M.	+	Urine	Miliary	...	118	D.	Spinal block on admission. Steady deterioration though miliary lung lesions cleared.
7	M.	1 $\frac{1}{2}$	14	M.	+	...	Enlarged glands	...	44	D.	Steady deterioration.
8	M.	10	9	M.	+	...	Enlarged glands	...	106	D.	Steady deterioration. Blindness after 25 days.
9	F.	10	14	E.	+	G.W.O.	Primary complex	...	258	-R.	Clinical and C.S.F. findings normal after 4 months' course. Treatment resumed following relapse at 227 days.
10	F.	15	...	E.	0	...	Negative	See remarks	224	D.W.	Treated following operative removal of cerebellar tuberculoma. C.S.F. findings indicative of meningitis.

11	F.	21 <sup>10</sup> <sub>10</sub>	28	A.	+	G.W.O.	Miliary	Choroidal tubercles ...	8	D.	No response.
12	F.	10	10	M.	+	G.W.O.	Primary complex	...	177	D.W.	No clinical evidence of meningitis now. Primary lung lesion still active.
13	M.	2 <sup>1</sup> <sub>14</sub>	7	M.	+	G.W.O.	Miliary	Choroidal tubercles ...	43	D.	Slight initial improvement. Followed by steady deterioration.
14	M.	14	16	M.	0	...	Negative	...	144	D.W.	Streptomycin administered before admission and case not proven bacteriologically, though clinically definite.
15	M.	5	13	M.	+	...	Enlarged glands	...	18	D.	Steady deterioration.
16	F.	14	20	A.	+	...	Negative	...	18	D.	Little response.
17	F.	22	21	M.	0	G.W.O.	Miliary	...	9	D.	Spinal block on admission with lower limb paralysis and urine retention.
18	M.	4 <sup>1</sup> <sub>13</sub>	10	A.	+	...	Primary complex	...	8	D.	No response.
19	M.	13	7	M.	+	...	Bilateral pleural effusion	...	63	D.	Initial improvement followed by relapse.
20	F.	12 <sup>1</sup> <sub>4</sub>	22	A.	+	...	Miliary	...	1	D.	Moribund on admission with spinal block.
21	F.	4	13	E.	0	G.W.O.	Primary complex	...	76	D.W.	No present clinical evidence of meningitis.
22	F.	4 <sup>1</sup> <sub>5</sub>	11	M.	+	...	Primary complex	...	68	D.W.	No present clinical evidence of meningitis.
23	F.	5	3	E.	+	...	Negative	T.B. knee. Calcified abdominal glands	61	D.W.	No present clinical evidence of meningitis.
24	F.	19	10	M.	+	...	Bilateral apical foci	...	51	D.W.	...
25	M.	1 <sup>4</sup> <sub>28</sub>	2	M.	+	...	Miliary	...	50	S.	Block on admission.
26	F.	28	18	M.	0	...	Negative	...	40	D.W.	No present clinical evidence of meningitis.
27	F.	28	?	M.	0	...	Bilateral apical	Cerebellar tumour ? Tuberculoma	45	D.W.	Sub-occipital decompression has been performed.

E.—Early. M.—Moderate. A.—Advanced. GWO.—Gastric Washout. DW.—Doing well. S.—Stationary. R.—Relapse.

It is of interest to know the period of survival both of those cases who have died and those who remain alive. This information is illustrated in graphic form in Fig. 1.

It is apparent that a large proportion of the deaths occurred in the early months of treatment—many of these within the first twenty days. The longest period of survival among the mortalities has so far been 256 days. Of those who survive the majority are still at a comparatively early stage of treatment and it is to be expected that a proportion of these will ultimately succumb. Our longest survivor has now been alive for 389 days since treatment was instituted. He merits some description and is described later.

On admission the cases were classified according to the stage of the disease and as criterion we adopted the degree of consciousness. It was found that our classification bore only a rough relationship to

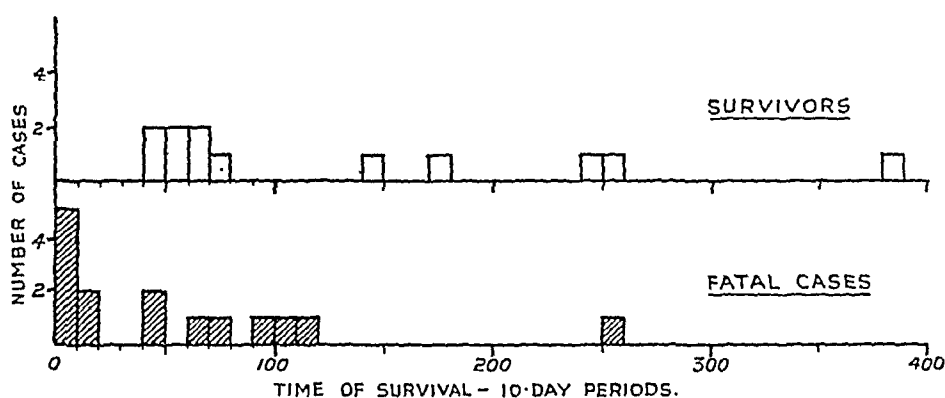


FIG. 1.

the estimated duration of the disease prior to admission. Cases were classified as follows:—

*Early*.—Irritable but not confused and without any paralytic signs.

*Advanced*.—In deep coma. Barely able to be roused.

*Moderate*.—The remaining cases were placed in this category. These cases were confused but not in deep coma. They exhibited a variety of neurological signs and many of them would, in the normal course, have been considered advanced. Thus of 5 cases showing manometric evidence of spinal block on admission 4 were classified as “moderate” and one as “advanced.”

Table III shows the results obtained in these different classes. As one would expect the best results have been obtained with the early cases while advanced cases have borne the worst prognosis.

The results in different age groups are shown in Table IV. As in reports of larger series the age group up to three years has shown the highest mortality.

Finally, cases can be classified according to whether or not a “snow storm” lung was present on admission (Table V). In cases

exhibiting this combination the results of streptomycin treatment have been disappointing.

DIAGNOSIS.—As these results indicate the early diagnosis of tuberculous meningitis is now a matter of considerable urgency.

TABLE III

*Meningitis Admissions before 30th September Assessed on 31st October  
Results Related to Stage of Disease on Admission*

State of Disease.	Number of Cases.	Deaths.	Doing Well.	S.R.D.
Early . . .	5	1	3	1 (R)
Moderate . . .	17	9	7	1 (S)
Advanced . . .	5	5	0	0
Total . . .	27	15	10	2

TABLE IV

*Results Related to Age Groups*

Age in Years	Number of Cases.	Deaths.	Doing Well.	S.R.D.
0-3 . . .	5	4	0	1 (S)
4-16 . . .	17	9	7	1 (R)
17+ . . .	5	2	3	0

S—Stationary

R—Relapse

D—Deteriorating

TABLE V

*Results of Streptomycin Treatment of Tuberculous Meningitis*

	Number of Cases	Dead.	Doing Well.	S.R.D.
With "snow-storm" lung .	8	7	0	1 (S)
Other cases . . .	19	8	10	1 (R)
Total . . .	27	15	10	2

Where the neurological and laboratory findings do not permit an immediate confident diagnosis we have found two lines of investigation particularly useful. The first of these is the search for other tuberculous stigmata and an immediate chest X-ray should be a routine. In our series the chest X-ray has been positive in 22 out of the 27 patients. Of these 22 patients, 8 showed a "snow storm" lung, 5 showed a

recent primary complex and one (a child aged 2) a calcified complex : in 3 there was hilar glandular enlargement without any obvious lung focus, 3 showed bilateral apical tuberculosis of hæmatogenous type, one had an "adult type" infiltration of one lung and one a bilateral pleural effusion. Of the remaining 5 cases one had a tuberculous knee and calcified abdominal glands and in one there was a history of recent removal of a cerebellar tuberculoma. In only 3 cases did we fail to find some evidence of tuberculosis elsewhere. Of these 3 cases 2 were aged 14 and one was aged 20 years, so that in the younger age groups we have always found collateral evidence of tuberculosis.

The other investigation which we have found useful is the Mantoux test. It is commonly said that this reaction is frequently negative in the presence of meningitis, but our experience has not borne this out in respect of patients tested on admission, though admittedly the results might be different if the testing were done at a more terminal stage. Twenty-five cases were tested and all were positive reactors except one who did not react to 1/100 O.T. Obviously the tuberculin test has its most useful function in the young child and in the presence of suggestive clinical and C.S.F. findings I would regard a positive Mantoux reaction in a child under the age of four as a sound indication for starting streptomycin treatment.

A history of contact was elicited in 6 of the cases. We took the opportunity of X-raying the mother of one other child and found previously unsuspected lung tuberculosis of long standing.

DOSAGE.—Originally the dosage we used was 2 gms. per day for an adult while for a child we gave 10-20 mgms. per pound body weight. Intramuscular injections were given at six-hourly intervals. Our dosage since March of this year has been modified to 1-1.5 gms. daily for an adult while intramuscular injections have been given at twelve-hourly intervals.

This scheme of intramuscular dosage has applied to all types of cases and in general cases have been treated for a period of approximately four months—some for shorter periods and some for longer. In one case treatment was given for only fifty-eight days and this patient is at present well. Meningitis cases all receive intrathecal treatment. It is our present practice to restrict the intrathecal dose to not more than 50 mgms. per injection. All cases on admission receive daily intrathecal injections for a period of two to four weeks, and thereafter a weekly intrathecal injection is given when C.S.F. is withdrawn for routine examination. Further intensive intrathecal courses are given only if relapse follows a period of improvement. In cases of spinal block intrathecal injections have been given intracisternally and in one case intraventricularly.

ASSESSMENT OF PROGRESS.—There is no doubt that the clinical condition of the patient affords the best guide to progress. The clinical appraisal includes a consideration of the symptoms and general

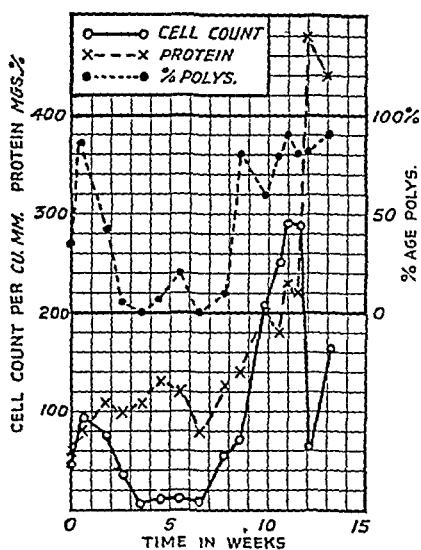


FIG. 2.—Case 4. Improvement, relapse, death.

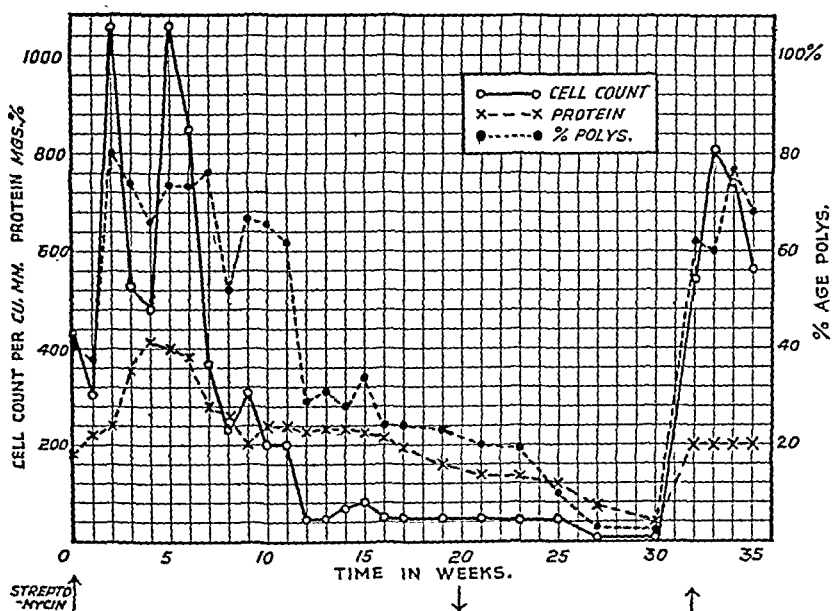


FIG. 3.—Case 9. Improvement, relapse.



condition of the patient, of his temperature, his mental state and the progress of paralyses. A failure to improve in any one respect must make one guarded about the eventual prognosis.

As a rule cases who are doing well show a fall in temperature and this is considered a favourable sign if associated with improvement in other respects. Usually the fall in temperature is appreciable within a week or two of admission but not always so: in our longest survivor, for example, the temperature did not reach a consistently normal level until twenty-seven weeks after admission.

On the other hand it is by no means uncommon to find a steady fall in temperature in patients who are going downhill and eventually succumb. Such a course is easy to understand if we remember that a fatal outcome may ensue from meningitis not merely as a result of active inflammation but due to the mechanical and vascular sequelæ of a meningitis which is healing.

We have found the E.S.R. of little value in assessing progress: it is frequently normal in cases who are moribund.

C.S.F. FINDINGS.—The C.S.F. findings are not easy of interpretation and, like the temperature, they should be correlated with the clinical progress. A study of the changes in cell count and protein is of some use, however, and certain trends are discernible. It is important that cell counts—both total and differential—be done on fresh specimens of C.S.F.

The C.S.F. changes in some of the meningitis cases are shown (Figs. 2-5). The cells indicate the activity of meningeal inflammation, active progressive meningitis being shown by a high or rising cell count, of which a high proportion—often the majority—are polymorphs. Conversely a healing meningitis is associated with a falling cell count, and a low or decreasing percentage of polymorphs. Such a trend need not necessarily foretell a favourable outcome, as the mechanical sequelæ associated with cicatrisation and healing may, in themselves, produce clinical deterioration and death (Fig. 5). In such a case the C.S.F. protein level shows a steady and pronounced rise. In a favourable case the protein level, after an initial increase, shows a gradual fall.

Our experiences so far indicate, therefore, that a combination of falling total cell count, polymorph percentage and protein level in the C.S.F. is a hopeful sign.

#### ILLUSTRATIVE CASES

CASE 3.—D.H., male aged 15. This patient worked in a slaughter house and it is of interest that he is the only case of our series in whom the infecting organism has been shown to be of bovine type. On admission on 10.10.47 he was very confused and inattentive with marked spasticity. A complete paralysis of all movements of the right eye was present and there was also a left facial weakness. Plantar responses were extensor and all tendon reflexes were exaggerated. Improvement was gradual. Three weeks after admission

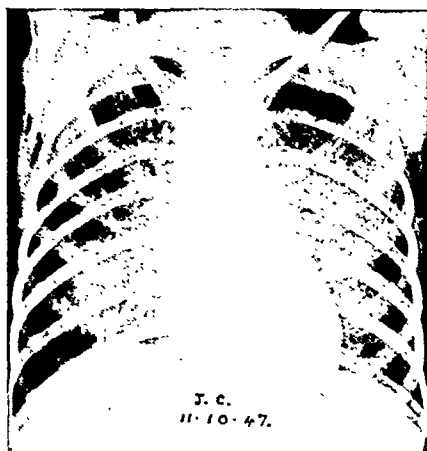


FIG. 6

Case 4. 11/10/47. Gross miliary tuberculosis.

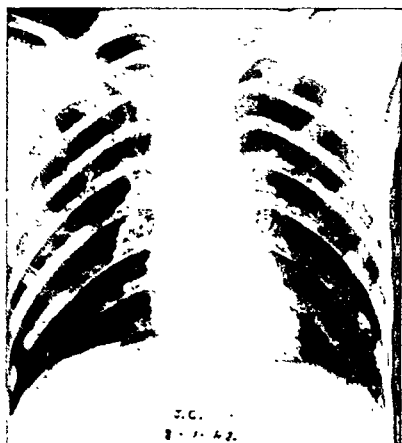


FIG. 7

Case 4. 8/1/48. Marked clearing. Death from meningitis.

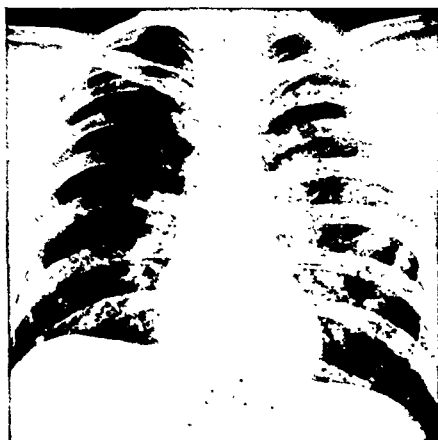


FIG. 8

Case D. Well-developed miliary tuberculosis.

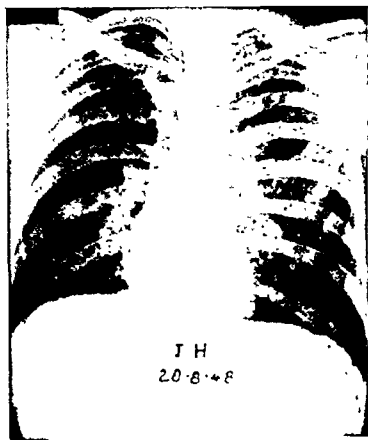


FIG. 9

Case D. After 3 months' streptomycin. Little improvement.



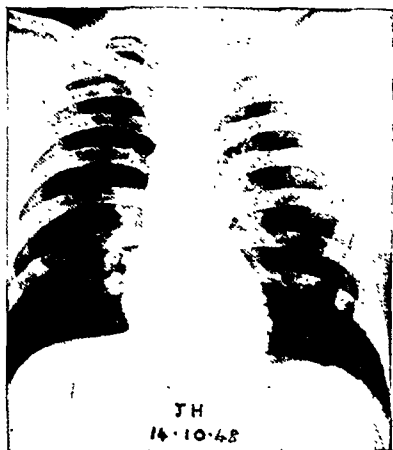


FIG. 10

*Case D.* Marked clearing after 6 weeks' treatment with streptomycin and sulphathione.

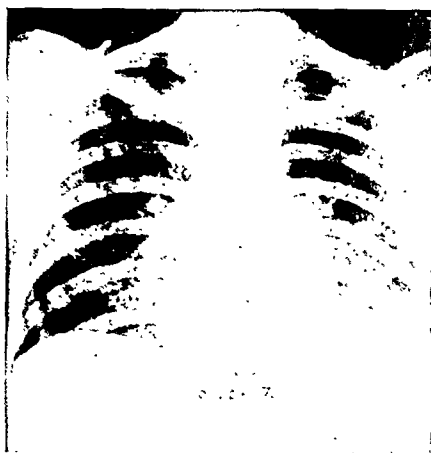


FIG. 11

*Case C.* Miliary tuberculosis. Left basal effusions.

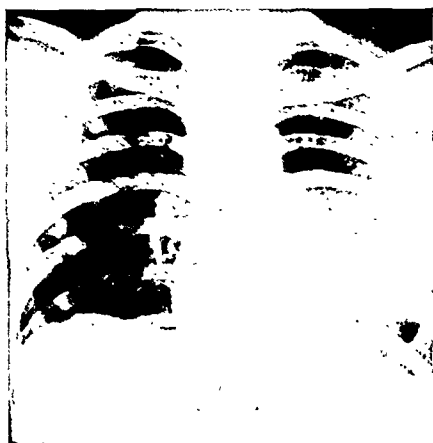


FIG. 12

*Case C.* At termination of streptomycin treatment. Improved but parenchymal lesions still present.

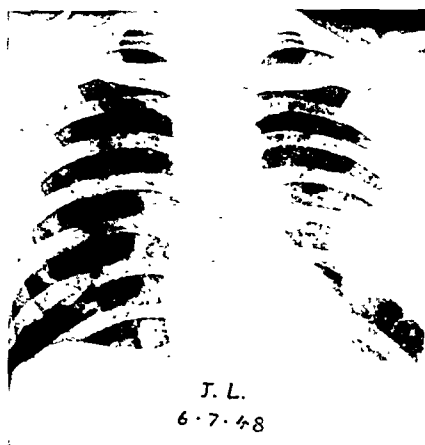


FIG. 13

*Case C.* Three months later. Lung fields clear. Residual pleural thickening.



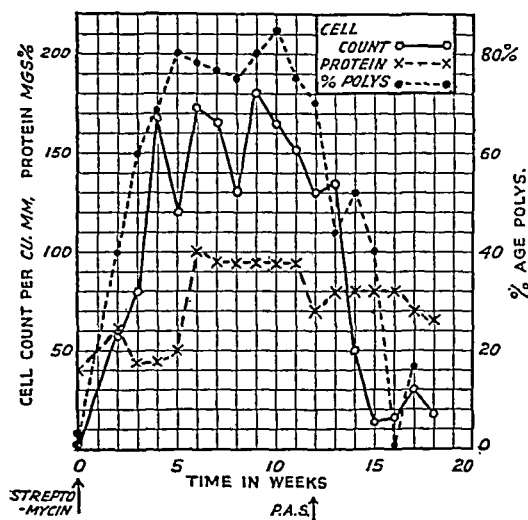


FIG. 4.—Case "E." Delayed improvement. Streptomycin combined with Paramisal Sodium.

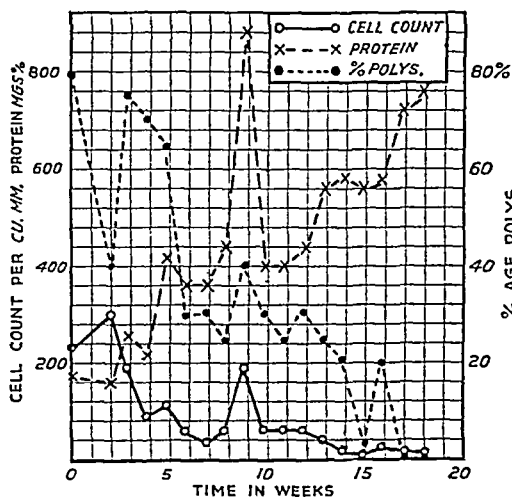


FIG. 5.—Case 6. Deterioration, death.

he developed a Froin syndrome and the C.S.F. protein reached as high a level as 5900 mgms. per cent. Despite this complication clinical improvement was maintained.

This patient is now up and about for several hours daily. The Froin syndrome persists with a C.S.F. protein of 1000 mgms. and cisternal puncture gives a dry tap. Apart from clumsiness of gait, a tendency to stumble and exaggeration of the tendon reflexes, neurological examination is normal and he has suffered slight, if any, mental impairment.

CASE 4.—J.C., female aged 13, was highly febrile at the time of admission (11.10.47). She was grossly underweight and was dyspnoëic and cyanosed. Chest X-ray showed dense miliary shadows and multiple choroidal tubercles were visible. The spleen was enlarged. Apart from slight irritability, neck rigidity and Kernigism, C.N.S. examination was normal.

Her initial response to treatment was good. After a month her spleen was no longer palpable, choroidal tubercles were healing and chest examination showed few accompaniments where râles had been numerous before. C.N.S. examination at that time was quite negative and the C.S.F. findings had shown a definite improvement.

Two months after her admission headache and vomiting returned. Despite further intrathecal treatment the signs of basal meningitis progressed and she died on 13.1.48.

Throughout the course of her illness there was steady improvement in the chest X-ray appearances (Figs. 6 and 7). The C.S.F. changes are shown in Fig. 2.

CASE 9.—P.W., female aged 10, was admitted on 16.2.48. Although she had had symptoms for two weeks before admission we regarded her as an early case. Her chest X-ray showed a primary complex in her right upper lobe.

During the first ten days her temperature showed a steady drop to near normal and then suddenly rose to  $102^{\circ}$ . This was associated with a deterioration in the C.S.F. findings. Thereafter there was a gradual clinical improvement and when streptomycin treatment was discontinued this patient appeared to be normal in all respects. Chest X-ray had shown resolution and neurological examination was quite negative while the C.S.F. findings became normal (Fig. 3). Relapse followed, however, and she has been under treatment again since 4th October.

CASE 10.—J.H., female aged 15. This case was not bacteriologically proven but the evidence of tuberculous meningitis was strong and the case is described because it differs in many respects from the normal type of case. She was admitted to the neuro-surgical unit at Bangour on 25.2.48. For two months previously she had suffered from headache and she had been giddy for two weeks. Lumbar puncture on 23.2.48 had given a clear fluid under 350 mm. pressure containing 5 cells per c.mm. and with a protein content of 100 mgms. per cent. A diagnosis of cerebellar tuberculoma was made and operation was undertaken on 26.2.48. A specimen of lumbar C.S.F. immediately prior to operation showed a cell count of 25 per c.mm. and protein content of 80 mgms. per cent. This finding suggests that meningitis may actually have been present before operation was performed.

At operation it was found impossible to remove the tumour in one piece

and caseating tissue was exposed. The histological appearances subsequently confirmed that the tumour was a tuberculoma.

Under these circumstances tuberculous meningitis seemed inevitable and treatment with intrathecal streptomycin was begun. Unfortunately, owing to an oversight, a pre-treatment specimen of C.S.F. was not cultured or inoculated into a guinea pig.

For the first seven days streptomycin was administered by the intrathecal route only and during that period the C.S.F. findings showed a deterioration with rising cells, falling sugar and falling chlorides. This was regarded as good corroborative evidence of tuberculous meningitis and combined intramuscular and intrathecal treatment was begun on 4.3.48. The whole course of treatment given lasted fifty-eight days. This patient still shows signs of cerebellar deficiency but she is up and about and the C.S.F. findings are now normal.

CASE 12.—M.C., female aged 10, admitted on 8.5.48 was confused and irritable on admission with a tendency to lapse into stupor. There was marked neck rigidity and Kernigism and there was bilateral sixth nerve paralysis. A moderate degree of papilloedema was present. Chest X-ray showed enlargement of the right hilar shadow.

This girl's response to treatment was again rather slow. A few days after admission a left facial weakness became apparent but disappeared after a week. When streptomycin treatment was discontinued after four months this patient showed no clinical evidence of meningitis and the C.S.F. findings were also satisfactory. She remained, however, slightly febrile and chest X-rays showed a spread of disease in the right lung during the first month after cessation of treatment.

In this case, therefore, a period of four months streptomycin treatment did not bring about healing of the primary lung complex. The same failure of streptomycin to induce healing of a caseating primary complex, while the smaller disseminated lesions elsewhere regress, has been demonstrated at post-mortem examinations of some of our cases.

### MILIARY TUBERCULOSIS

The results in cases showing miliary disease without meningitis on admission have so far been considerably better than in the meningitis series.

Of the total of 8 \* cases with acute miliary tuberculosis only one has died to date and the others are progressing favourably. The one death was due to meningitis. It is our practice to examine the C.S.F. of all miliary cases on admission and at regular intervals thereafter. It is interesting to note that of the total of 8 cases no less than 4 have

\* One further case is excluded from the analysis as the miliary tuberculosis was not regarded as typically acute. The patient aged 57, died with signs of liver failure due to cirrhosis following infective hepatitis. Post-mortem confirmed the liver damage and showed scanty, healing miliary lung tubercles. Miliary tuberculosis was not regarded as contributing directly to her death.



subsequently developed C.S.F. evidence of meningitis. In 2 of these cases clinical evidence of meningitis has not developed to date.

CASE B.—M.G., female aged 14, was notified to the unit as suffering from miliary tuberculosis on 2.3.48. We were unable to admit her until 12.4.48, *i.e.* over a month later. On admission she was pale, thin and febrile with enlarged liver and spleen. Her chest X-ray showed a typical "snow storm" appearance.

Ophthalmoscopy showed bilateral papilloedema of moderate degree and miliary choroidal tubercles were noted. There was a fine nystagmus on looking to either side but in other respects neurological examination was negative. A C.S.F. cell count was normal but the protein was raised to 70 mgms. per cent. A tentative diagnosis of cerebellar tuberculoma was made. With intramuscular streptomycin treatment her general condition showed a steady improvement but on 8.5.48 vomiting began and persisted and the C.S.F. on 13.5.48 showed a raised cell count. Intrathecal streptomycin was begun and four days later she was transferred to the neurosurgical unit where a sub-occipital decompression was performed. During the operation the presence of a cerebellar mass was confirmed.

For a period thereafter she continued to make steady headway in all respects. Chest X-ray appearances reverted to normal limits and the liver and spleen enlargements disappeared. Streptomycin treatment was discontinued on 3.8.48. A month later vomiting returned together with a rise in temperature and deterioration in the C.S.F. Streptomycin treatment was resumed and the clinical response noted so far has been satisfactory.

CASE C.—Male aged 22. At the time of admission on 10.12.47 he was thin and toxic with a temperature of 102°. Chest X-ray showed a rather coarse miliary tuberculosis with a small left basal effusion (Fig. 11).

He made a satisfactory clinical response to streptomycin treatment but at the time of completion of treatment his chest X-ray, while improved, was not clear (Fig. 12). A subsequent X-ray taken three months after cessation of streptomycin treatment showed further clearing, only residual pleural thickening being evident (Fig. 13). This patient remains well.

The interest in this case lies in the continued improvement after cessation of streptomycin. It would appear that in an acute infection streptomycin affords a period of respite during which the natural defence mechanisms of the body may be mobilised and brought into action.

It would be easy for me to give further illustrations of the dramatic clearing of radiological miliary shadows on streptomycin treatment. We have ceased to be unduly impressed by such an occurrence and are now more interested when streptomycin fails to produce such a response.

CASE D.—J.H., male aged 16, was admitted to this unit on 28.5.48. He was admitted to hospital elsewhere with unexplained fever on 12.5.48. Chest X-ray showed a primary lung complex. Fever persisted and a repeat chest X-ray showed definite miliary tuberculosis.

The X-ray film of the patient at an early stage of treatment is shown (Fig. 8). After fourteen weeks' streptomycin treatment he was still febrile and his weight had shown a fall from 9 st. 8 lbs. to 8 st. 9 lbs. Chest X-ray showed little improvement (Fig. 9).

On 4.9.48 we began a course of sulphetrone in addition to streptomycin. This period of sulphetrone treatment has coincided with a dramatic improvement. During six weeks of sulphetrone therapy his weight increased by 15 lbs., his B.S.R. fell and radiologically there was a marked improvement (Fig. 10).

CASE E.—B.H., female aged 5, admitted on 22.6.48 showed advanced miliary lung disease with massive enlargement of mediastinal glands. C.S.F. examination was negative.

Streptomycin treatment was begun but no clinical response was noted and she remained febrile. A repeat C.S.F. examination on 6.7.48 showed changes indicative of meningitis and intrathecal streptomycin was begun. Throughout there has been no clinical evidence of meningitis except for occasional vomiting, but the C.S.F. findings (Fig. 4) showed for a long period, no sign of improvement while the response in the chest radiological findings was also disappointing. After twelve weeks, treatment with Paramisal sodium by mouth was instituted and for a further six weeks she received both streptomycin and P.A.S. Improvement in the C.S.F. findings followed and her latest X-ray shows the miliary lesions smaller and less obvious though there is still very marked glandular enlargement. We have now stopped all treatment in this case to observe the effect.

It is not claimed in these last 2 cases that the improvement was due to sulphetrone or P.A.S. Quite possibly it was co-incidental but it is our intention now to try a series of cases with a combination of drugs.

Before leaving miliary disease and meningitis and considering pulmonary tuberculosis there are one or two features which merit discussion. It is frequent to find that miliary tuberculosis responds as judged by the chest X-ray findings while at the same time a coexistent meningitis pursues a fatal course. This apparently contradictory effect is understandable where death results not in direct consequence of meningitis but because of its sequelæ. In other cases the modern conception of the pathogenesis of tuberculous meningitis provides a ready explanation.<sup>5</sup> Streptomycin is not demonstrable in brain tissue and a caseous focus there may therefore remain untouched by streptomycin and lead to renewed invasion of the meninges. The same conception explains the comparative rarity, in contrast to experience with pulmonary tuberculosis, with which streptomycin resistant organisms are isolated from the C.S.F. of meningitis cases under treatment or after relapse (so far significant streptomycin resistance has not been detected at Bangour in any case of meningitis). It also provides a possible reason for the inferior results where meningitis is associated with acute miliary tuberculosis: where a massive blood invasion has occurred there is a probability of more than one, perhaps

several, brain foci being present and the chance of repeated invasions of the meninges by bacilli are correspondingly increased.

### PULMONARY TUBERCULOSIS

A case of meningitis or acute miliary tuberculosis presents no difficulties as regards a decision to use streptomycin. In the case of pulmonary tuberculosis, the hard core of the tuberculosis problem, the decision is by no means so simple.

At Bangour 3 pulmonary cases received treatment and they are included in the M.R.C. report recently published. The type of case treated under that investigation was defined as "acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, age group fifteen to twenty-five years."

TABLE VI

*Pulmonary Cases Treated by Streptomycin. Period of Treatment Four Months*

Period in Months.	Sputum Smear for T.B.	Weight in Pounds.	Temperature.	Hæmoglobin Percentage.	B.S.R. in mm./hr.	
0	+++	86	103.4	67	98	Case 1
2	-ve	93	100.4	79	50	
4	+++	88	100.8	73	68	
6	+++	88	101.1	77	78	
0	+++	94½	101.7	76	70	Case 2
2	-ve	102	99.2	98	30	
4	+	106	99.5	87	40	
6	-ve	116	99.4	88	8	
0	++	131½	99.8	96	66	Case 3
2	+ (scanty)	128	99.2	116	17	
4	+	126	100.2	97	40	
6	++	123	99.3	102	24	

Temperature—Mean evening rectal temperature for one week.

All 3 cases remain alive fifteen to seventeen months after their admission. In 2 cases (Case 1 and Case 3) the ultimate progress remains poor, while in one the outlook for the future is reasonably good.

During the four-month period of treatment each case showed a radiographic improvement which could be described as moderate or marked. The maximum improvement was noted in the first two months: during the last two months of treatment the X-ray appearances were either stationary or showed slight improvement. A similar trend was appreciable in respect of the clinical and laboratory findings—improvement mainly in the first two months; slight improvement or even deterioration in the second two months (see Table VI). After cessation of streptomycin a period of improved well-being was noted though this was short-lived in case 1 who developed a spread of disease in the fifth month. In all 3 cases organisms resistant to high

concentrations of streptomycin became evident during the period of treatment.

No conclusions can be drawn from a study of such a small number of cases but I am left with the impression that a shorter period of treatment might have been just as effective and possibly more effective.

**LIMITATIONS OF STREPTOMYCIN.**—This leads me on to a discussion of that important point—the limitations of streptomycin in the treatment of pulmonary tuberculosis. It is now well established that little benefit can be expected from the use of streptomycin in the chronic case where fibrosis dominates the picture (nor can it be expected that any further therapeutic agent will necessarily be more successful). In this type of case the natural healing reactions which have already occurred constitute a barrier to further healing. Cavities are surrounded by thick caseating and fibrotic walls; bronchial distortion is frequently present and limits effective drainage of diseased areas. Although it is probable that streptomycin is able to penetrate caseating and fibrotic tissue, the effectiveness of streptomycin is diminished considerably in an acid environment such as is found in caseating tissue.

Further barriers to the effectiveness of streptomycin lie in the toxicity of the drug and the emergence of resistant organismal strains. The main toxic effect is exerted on the eighth nerve. In 15 of the cases at Bangour it has been possible to carry out regular tests of vestibular function and hearing. In all of these cases vestibular function, as judged by caloric tests, has been lost. With the exception of one case, whose caloric response returned five months after stopping treatment, there has been no recovery to date. Three cases developed a high tone deafness which persists.

Whilst it is true that patients appear to compensate adequately in due time for the loss of vestibular function this toxic effect cannot lightly be dismissed. It is probable, for instance, that patients would have trouble in negotiating the cobbled streets of Edinburgh in the dark. Best and Taylor, in their physiology textbook, point out that a deaf mute with undeveloped labyrinths will flounder helplessly, even though he is a good swimmer, if he is put into deep water, as the optical and other righting reflexes cannot then come into action.

By itself this feature of neuro-toxicity would be sufficient to render undesirable the use of streptomycin in cases of tuberculosis where a cure by other means might be expected. The factor of drug resistance is an even more cogent reason why streptomycin treatment should be withheld in that type of case.

It has now been clearly demonstrated that drug resistance does not develop as a consequence of metabolic adaptation on the part of the organism but that it is due to a process of selection of naturally occurring resistant variants. A so-called resistant strain of tubercle bacilli in reality comprises a group of heterogeneous organisms exhibiting differing degrees of streptomycin sensitivity.<sup>6</sup> At present

(and long may it continue) the organisms are predominantly sensitive but as streptomycin treatment disposes of those sensitive organisms the originally resistant ones are unmasked. Whether they will multiply sufficiently to nullify the effectiveness of streptomycin will depend on two factors, namely, the number of infecting bacilli and that factor, difficult of assessment—the resistance of the patients to the disease. The larger the number of infecting bacilli the larger the number of originally resistant organisms capable of multiplication: the greater the resistance of the patient the more possibility is there of the multiplication of these resistant bacilli being checked with maintenance of the healing process.

Drug resistance, once apparent, seems to be permanent and it is obviously of importance both from the view point of the community and from the view point of the individual patient. Not only may streptomycin be ineffective where bacilli are resistant; there is a possibility that it may serve to activate the infection. It has indeed been shown that some organisms are *dependent* on the presence of streptomycin for full growth.<sup>7, 8</sup>

These shortcomings, toxicity and organismal resistance, have led to investigations of the effects of shorter courses with smaller doses. The present evidence suggests that a course of 1 gm. daily for six weeks is as effective clinically as a longer course with heavier dosage and such a course causes vestibular disturbance much less frequently. Since organismal resistance usually becomes apparent after two to three months this course can be given without resistant organisms revealing themselves. There is, however, evidence that in a second course, even after an interval, resistant organisms will emerge at a correspondingly earlier stage.

Our present knowledge, therefore, indicates that the patient with lung tuberculosis will be benefited fully only once in the course of his illness by a course of streptomycin. It is therefore important to consider under what conditions streptomycin will be most effective. The best response is afforded by the recent acute type of lesion where caseation necrosis has not yet developed to any extent. Our most common sanatorium inmate, the patient with fibro-careous lung disease, will, with certain exceptions, derive little real benefit, though temporary symptomatic improvement may ensue from the effect on small fresh extensions in the vicinity of the main disease. The exceptions are important. The effect of streptomycin on fresh lesions makes it a valuable weapon in the acute episodes which might otherwise worsen irrevocably the prognosis for the individual. Such episodes include the post-hæmoptoic dissemination, and extension of disease following therapeutic collapse. It will widen the scope for lung surgery both in consequence of its effect on parenchymal disease and its effect on tracheo-bronchial tuberculosis. Finally, we must not forget its valuable palliative effects in some of the more distressing sequelæ of lung

tuberculosis—ulcerative disease of the larynx, oropharynx and intestines.

These considerations make it obvious that streptomycin while by no means the ideal chemotherapeutic agent so long awaited, has yet potentialities unsurpassed by any previous tuberculostatic drug. Its proper use demands knowledge and foresight on the part of the physician and a real understanding of the complexities and possible courses of lung tuberculosis. A wise physician, like a good general, plans ahead. He considers possible developments and arranges his therapeutic armanentarium accordingly. With such a weapon as streptomycin he will be careful not to fritter it away in a minor skirmish but he will reserve it for an action in which its use may be decisive.

The streptomycin for the pulmonary cases was supplied by the Medical Research Council. The Faculty of Medicine of Edinburgh University selected Bangour as a centre for treatment of miliary and meningeal tuberculosis, streptomycin for that purpose being supplied by the Department of Health. I am indebted to Dr McAlister, Medical Superintendent of Bangour, for the facilities which he provided. I have been very fortunate in having the help and advice of Professor Dott and his staff, and of Professor Cameron. Dr Urquhart and Dr Weir, under the supervision of Dr Ewart Martin, carried out the tests of cochlear and vestibular function. Mr White was responsible for the X-ray reproductions. Heavy demands fell on Dr Purdie and the laboratory staff, and I am most grateful to them. Finally, I should like to express my thanks to the resident doctors and nursing staff, who have co-operated so well and willingly.

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#### ADDENDUM

The state of the patients forming the material for this paper was re-assessed on 10th March 1949 and the results to date are as follows :—

##### PATIENTS WITH MENINGITIS ON ADMISSION

(Minimum observation period 170 days)

Of the 27 cases the number of deaths remains 15 and all the 12 remaining cases are now doing well. Two patients have been discharged from hospital.

## MILIARY CASES

Of the eight cases four have developed meningitis during treatment and the diagnosis of meningitis and another patient, with meningitis, is deteriorating although the chest X-ray is normal. The six remaining patients are doing well and two of them have been discharged.

## PULMONARY CASES

Of the three cases, one is dead, and one is in poor condition. The remaining case has been discharged from hospital well and sputum negative.

## DISCUSSION

*Professor Cameron* said that he had listened with the greatest interest and admiration to the talk which Dr Ross had given, and asked to be allowed to refer to some of the points which Dr Ross had already discussed and to discuss briefly other conditions which he had not mentioned.

The ordinary physician who has not had time to keep himself in touch with the literature of streptomycin wants to know primarily what types of tuberculosis benefit from the treatment. Dr Ross referred to Rich's theories on the pathogenesis of tuberculous meningitis. These views are generally accepted and they have been confirmed, among other workers, by Dr Agnes Macgregor. In a majority of cases meningitis has been found to be due to the eruption of a caseating tuberculous focus in the cerebral cortex, and Dr Ross's suggestion that the refractoriness of some cases of meningitis to treatment, and the relapses which occur in other cases, are probably due to the persistence of the original focus which has not been affected by the streptomycin is probably correct. In 1947 an interesting paper was published by Baggenstross, Feldman, and Hinshaw. This article gave a detailed description of the histological findings in 5 cases of miliary and meningeal tuberculosis which had died after treatment by streptomycin. The duration of treatment of these patients varied from five to ninety-two days and in all, except the patient who survived for five days only, there was definite evidence of healing in many of the lesions, particularly in the miliary tubercles of the lungs, liver, and spleen. Dr Ross showed an exactly similar slide. The point of interest in this paper was that there was an absence of significant histological signs of regression in the lesions of the primary complex of the lungs and hilar glands in 3, in the hæmatogenous lesions of the kidney in 2, in the prostate gland in 2, in the adrenal glands and bladder in 1, and in the meninges in 4. In defining their conclusions the authors state that the size of the mass of the lesion at the time when treatment is begun has a very definite influence upon the probable ultimate result. Streptomycin can be expected to exercise some influence upon the early miliary lesions whereas the larger caseating lesions are unlikely to be affected. A second factor of influence is the known variation in the concentration of the drug in various body tissues and fluids. The drug does not enter the brain tissues although it does reach the cerebrospinal fluid in small quantities. We see here some general indications for its use. Recent young tuberculous lesions are likely to benefit, and miliary tuberculosis very often undergoes apparent clearing with the drug. A varying percentage of meningeal cases is improved, recent figures placing the total of

temporary cures at around 30 per cent. The probability of permanent cure depends among other things upon whether the initial focus from which the dissemination has taken place has been affected by the drug. If, as often happens, a large caseating focus of infection remains unchanged a recurrence of dissemination may take place. These two conditions, from the pathological point of view, are probably the ideal conditions for the use of streptomycin.

There is no doubt that the drug will often clear up the acute exudative element in lung tuberculosis. In the recent report of the Medical Research Council on the streptomycin treatment of acute bilateral pulmonary tuberculosis a bigger percentage of cases improved in the streptomycin group than in the control group. None of these cases could be classed as permanent cures, and although the three cases which Dr Ross referred to all showed in varying degrees some clearing of the exudative shadows they still showed persistence of the underlying caseating and excavating lesions. It is difficult to believe that any permanent result can be hoped for in chronic pulmonary tuberculosis. This condition at any one time is a composite of various pathological states. The drug will affect the recent disseminations and spreads which are so common in this disease but it is unlikely basically to affect the older chronic tuberculous lesions. It does fortunately exercise a favourable effect on ulcerative lesions of the larynx and intestine and it is probable that it will find a useful field in the palliative treatment of these conditions even if the treatment is not curative of the lung disease.

It also has a definite action on tracheo-bronchial tuberculosis. This condition has come very much to the fore within recent years and it is responsible for some of the most difficult problems in the treatment of lung tuberculosis. All of us are familiar with the tension type of cavity which very often blows up to a larger size under pneumothorax treatment, is unaffected or made worse by phrenic paralysis, and is often not closed by thoracoplasty. This condition is recognised in America as one of the indications for removal of the lobe or lung. The tension of the cavity is due of course to a relative obstruction of the bronchus which allows air to pass on one direction—during inspiration—and one cannot expect the ordinary methods of retractile collapse to have any influence upon a cavity whose inflation depends upon this type of bronchial obstruction. It is hoped that a partial solution of the difficulties of its surgical treatment will result from the use of the specific action of streptomycin on the bronchial lesions.

The drug has also been used as a so-called umbrella for major thoracic surgery. Its action upon early lesions is undoubtedly a help in preventing, and in dealing with, spreads of disease which do sometimes take place after thoracoplasty operations.

There are no figures in this country dealing with results in genito-urinary tuberculosis. The Council of Pharmacy and Chemistry which reported in November 1947 on the results of streptomycin in the trials of the Veterans' Administration in America published the results of its use in 13 cases of genito-urinary disease. Although the drug appeared to exercise no effect upon gross caseating renal lesions it did have a favourable influence upon bladder ulceration, on small lesions of the epididymes, etc., and on sinuses. It is likely that the surgeon will find help from its use in this troublesome condition. The drug of course is excreted almost entirely by the kidney and its greatest concentration is found in the urine.



The dangers of streptomycin have perhaps been over-emphasised but the constancy with which it affects vestibular function is well recognised. Loss of vestibular function, when it occurs, appears to be permanent. Although it may be a small penalty to pay for cure in a fatal form of tuberculosis such as miliary disease, it is too big a price to pay for cure of an early tuberculous lesion which could have been cured by other means. We should be careful then in defining the indications for the use of streptomycin, and we should not resort to its use in early tuberculosis of the lungs or other areas for which we can offer a reasonable prospect of cure by existing methods. This is particularly important in the case of lung disease, as the danger of production of resistant strains of the organism with which Dr Ross has dealt is too obvious to need elaboration.

In the early days of streptomycin treatment daily doses of 2-3 gms. were employed. More recent experimental work suggested that the dose could be reduced and that frequent administration was not necessary for effective action of the drug. There has been a tendency within the past twelve months to reduce the daily dosage to 1-1.5 gms. given in two doses at twelve-hourly intervals. There is also some evidence that the smaller dose has no action on the vestibule.

Whether caronamide will have any field of usefulness with streptomycin is doubtful. In fact it is not yet known whether streptomycin is excreted by the renal tubules or not.

Dr Ross referred to the use of sulphethrone in combination with streptomycin. Professor Cameron had yet to be convinced that sulphethrone alone has any useful effect upon tuberculosis, and its hæmolysing effect makes it a dangerous drug to use. There is, however, good evidence that it exercises a synergistic effect with streptomycin and it is possible that the combination of these drugs may be helpful. Its success in his one case in combination with streptomycin may not have been accidental.

Para-amino-salicylic acid is an interesting drug. It was elaborated on a rational basis, but its sphere has not yet been defined. Professor Cameron had tried it in Southfield Sanatorium on 10 patients. It gave rise in all of them to a period of initial improvement, objective and subjective, but some have shown a tendency to regression after about two months of treatment. One man only has been definitely improved. He was a case with disseminated lesions and his improvement has been spectacular. It is possible that P.A.S. may prove useful as an adjunct to streptomycin.

When streptomycin is liberated it should be used with discrimination, and it would be a very wise thing to confine its use as far as possible to hospitals staffed by people who have some experience of it. Its limitations are obvious on theoretical and practical grounds, but it does represent a very big step forward in the treatment of tuberculosis. It is in fact the first drug which has been known to have any worth-while action on tuberculosis in the human subject.

*Professor Mackie* congratulated Dr Ross on his most interesting paper. Until recently all our present knowledge of the therapeutic action of streptomycin had been obtained from the American literature, and we valued, therefore, the opportunity of learning something more directly about this subject from one of our own colleagues in Edinburgh.

It was clear that streptomycin constituted a real advance in the treatment of certain forms of tuberculosis and that this substance could, under certain conditions, arrest the progress of a tuberculous infection. The limiting conditions in which therapeutic results could be obtained were of special importance. Certain of these conditions were not well known and had been referred to by the speaker, others were more obscure and a better knowledge of these would place us in a stronger position in the practical application of streptomycin.

In this connection, a factor of particular interest was the remarkable capacity of primarily sensitive organisms, including the tubercle bacilli, to become resistant to this substance. In certain work done in the University Department of Bacteriology this effect had been specially striking in the case of intestinal organisms following administration of streptomycin by the mouth. In fact, these organisms could acquire relative resistance to the antibiotic within two to three days. Of course, other antibiotics showed the same phenomenon but of those used up-to-date streptomycin exceeded all others in this respect. It was interesting to note that in Dr Ross's cases of meningitis the emergence of resistant strains had not been a specially pronounced feature, but the literature on streptomycin therapy of other tuberculous diseases showed very different results, and the development of resistant strains had been a frequent phenomenon. Recently attention had been drawn to the increasing prevalence of penicillin-resistant staphylococci and it had even been suggested that in the future, as regards the treatment of staphylococcal infections, we should be back to where we were before penicillin treatment was introduced.

Professor Mackie expressed the hope that the utmost caution would be exercised by clinicians as regards the selection of tuberculous cases for treatment by streptomycin when this substance became more plentiful.

Another fact of particular significance in regard to this problem had recently come to light, namely, that not only might a strain be resistant to streptomycin but that it might also be "streptomycin-dependent" and grow better in the presence of streptomycin than in its absence, the antibiotic in this case promoting growth. If streptomycin were used in a case of tuberculosis due to such an organism the clinical condition might in fact be worsened. It almost appeared as if there was a masked growth factor in the streptomycin molecule, and studies of the chemical structure of streptomycin might even suggest this.

Professor Mackie emphasised the necessity for persevering in research for new chemotherapeutic antibiotics and other substances in the endeavour to build up, as it were, a large armamentarium of these substances so that where one failed in a particular case another might succeed, or that two or more of these might be combined.

*Dr Urquhart* said that when it was known that streptomycin had a toxic effect on the inner ear, it was decided to carry out a series of investigations on Dr Ross's patients. It was known, of course, that the vestibular part of the inner ear was damaged by streptomycin but it was not known how soon this occurred or how permanent the loss was.

The cochlear part of the inner ear was tested by an audiometer with which it was possible to put variable tones into the ear at variable intensity. A graph of the range of a person's hearing could then be drawn.

For testing the vestibular part of the inner ear, instead of syringing the ear with cold water—the previous method—the ear was douched at 86° F. The result was nystagmus for approximately two minutes in a normal subject. If no response was noted at 86° F. the temperature was dropped to 50° F. and finally the ear was syringed with iced water.

The results of these tests were that 3 patients showed loss of hearing but only in the high tones, mainly above conversational range, and that loss was permanent. So far as the vestibule was concerned, all showed absolutely no response after about two months treatment, even when syringed with iced water. Only one case showed any recovery of vestibular function at all. He did so spontaneously six months after treatment had stopped, and had full recovery within a month. This was not understood as the treatment had been the same as for the others.

A further test for the inner ear is the Galvanic test, which is a test of the function of the auditory nerve, rather than the vestibular end-organ. Unfortunately it was only possible to try this test on one patient as at present no portable Galvanic apparatus was available. This patient, however, had been tested at the Physiotherapy Department. One electrode is put behind the ear and one on to the hand and the current turned to 8-10 milliamps., when nystagmus is noted and there may be vertigo also. The interesting thing about this patient was that he definitely showed nystagmus so that this suggests that the auditory nerve has not degenerated, and in view of what Professor Cameron said about decreased dosage causing less toxicity, it sounds as if those treated with less dosage may get their vestibular function back again, or possibly even not lose it at all.

*Dr Fergus Hewat* advocated the need for a medical censor to the press as Professor Bramwell had done many years ago. Too much publicity was given to a drug before it was really in plentiful supply, thereby causing much distress to the doctor when pressed by anxious relatives to try the new remedy. Dr Hewat had recently experienced such an unfortunate happening.

*Mr Jeffrey* referred to the Medical Research Council report (April) on the treatment of tuberculous meningitis with streptomycin, and compared the survival rate in the M.R.C. series and Dr Ross's series. In the M.R.C. series of 105 cases 35 per cent. were said to be alive and in good condition after four months, whereas the figures presented by Dr Ross were less favourable. He wondered whether this could be explained by differences in the dosage technique. The M.R.C. suggested 2-3 gms. daily as against Dr Ross's 1.5 gms. daily; and an intrathecal injection every two to three days of 100 gms., whereas Dr Ross mentioned 50 gms. daily. Mr Jeffrey suggested that in streptomycin therapy large and frequent doses were to be preferred in order to prevent development of resistant strains. In the M.R.C. series resistance of the bacteria was not a noticeable feature—3 out of 22 strains tested. The M.R.C. report also made a point of the streptomycin level of the C.S.F. as a prognostic sign: as the meningeal process advances the barrier becomes more permeable and the content rises.

*Dr Ross*, replying, referred to Professor Cameron's statement regarding post-mortem reports from America. Experience at Bangour had been similar,

cases showing clearing of the miliary lesions while the primary complex was apparently unaffected. In respect of caronamide, he stated that, while nothing had been published to his knowledge concerning its use with streptomycin, he understood that the effect of caronamide had been tested by Dr Mary Barbour with negative results. Sulphethrone had caused no toxic effects apart from cyanosis in the case described by Dr Ross in his paper, but in other cases Dr Ross's experience had been similar to Professor Cameron's and sulphethrone treatment had been stopped because of brisk hæmolytic and symptoms of depression. Professor Mackie had discussed the question of resistance of organisms to chemotherapeutic agents and had stressed the necessity for a physician to go warily in the use of a new drug like streptomycin. Dr Ross endorsed this and quoted a case of which he had heard. A child's parent, suffering from early lung tuberculosis, had obtained streptomycin and received treatment with the drug. The child subsequently developed meningitis and the organism was resistant to streptomycin, the outcome being, of course, fatal. Dr Ross agreed with Dr Hewat that care should be used in advertising a drug in the press until it was plentiful. None appreciated this fact better than he did with regard to streptomycin as he had been in the most unenviable position of having to turn away cases because of the shortage of the drug.

In reply to Mr Jeffrey, Dr Ross stated that the discrepancy in the mortality figures as compared with the M.R.C. series might be explained by the differing observation periods. He understood that only some 15 per cent. of the M.R.C. cases were doing well a month or two ago. With regard to intrathecal injections he stated that with a dose of 100 mgms. one may get meningeal reactions. This dose had been used originally at Bangour but had been subsequently reduced to not more than 50 mgms. Intrathecal injections were given daily for two to four weeks on admission, and thereafter weekly. This scheme of intrathecal treatment was not so intensive as that used by some others but in the M.R.C. series the centres had differed widely in their regimes of intrathecal treatment and no significant variation in the results had been noted as between those centres giving prolonged intrathecal treatment and those giving relatively short courses.

With reference to the C.S.F. streptomycin content, Dr Ross said that while streptomycin is not demonstrable in brain tissue it does, of course, get into the C.S.F. In cases of miliary tuberculosis without meningitis, the C.S.F. concentration attained with intramuscular treatment was low—about 1-2 units per c.c.—but in the presence of meningitis the concentration is higher. For reasons not definitely understood the concentration of streptomycin attained by intramuscular injections in the C.S.F. increased after a course of intrathecal injections.

The M.R.C. had stressed a rising streptomycin level in the C.S.F. as indicating a bad prognosis. The results at Bangour tended to confirm this but Dr Ross did not think that the information thereby attained justified frequent streptomycin assays as a routine. The procedure for streptomycin assay is time consuming and the assessment is not an exact one. Because of this latter feature it is unjustifiable to draw conclusions from two consecutive streptomycin assays. Mr Jeffrey had pointed out that in the M.R.C. series a few meningitis cases had shown an emergence of organisms resistant to streptomycin. The M.R.C. series, however, was a much larger one than that treated at Bangour and while so far no cases had shown resistant organisms

it was to be expected that such cases would be encountered in the future at Bangour.

Finally, Mr Jeffrey had suggested that a larger dosage initially might be a more logical method of treatment. There was much to be said for this view point and the French workers had reported good results using very heavy dosage. Dr Ross stated that there results were, in some respects, unconvincing in that a large number of the cases were not proven bacteriologically, and he had been guided chiefly by the experience of the Americans.

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# Edinburgh Medical Journal

March 1949

## THE GENESIS OF PEPTIC ULCERATION

By IAN AIRD, Ch.M., F.R.C.S.

*From the Department of Surgery in the Post-graduate Medical  
School of London, University of London*

### INTRODUCTION

THERE has been a considerable increase in the incidence of peptic ulcer since the end of the first world war (Hurst, 1944) and probably an increased incidence in males over the age of forty (Tidy, 1944). The incidence-curve of peptic ulcer over the last half-century shows indeed many remarkable features. As Illingworth (1944) has shown, perforated peptic ulcer was almost unknown in Glasgow before 1890, but then began an increase which reached a sudden peak in 1940-41 by a final steep rise, falling somewhat thereafter; the peak was reached and passed just *before* the first heavy air attack on the city. In 1924 there were 191 perforations in Glasgow, in 1941 there were 615. During this period the population has remained fairly constant, and the Glasgow community is a closed one so far as its surgery is concerned. This Glasgow increase has affected duodenal ulcer almost exclusively; the incidence of gastric ulcer has not greatly altered throughout the period.

Tidy (1945) has produced substantially different figures from London; his findings are no less interesting than Illingworth's, but they are different in kind. In Tidy's London patients, gastric ulcer has been commoner than duodenal, but its preponderance has fallen gradually from 2.2 to 1.9. The incidence of gastric ulcer in men over forty rose slowly in the teens of the century, doubled in the twenties, and has remained stationary since, while in men under forty the trend has been much less dramatic. Tidy concludes that there is more than one group of etiological factors, operating differently in the two sexes and at different ages.

One other remarkable feature of the behaviour of duodenal ulcer in the present century has not to my knowledge been recorded. In the twenties of the present century, the commonest site of a duodenal ulcer submitted to operation was the anterior wall of the first part; to explain this site Wilkie advanced the theory of a jet of acid juice

A Honyman Gillespie Lecture delivered in the Royal Infirmary, Edinburgh, 20th May 1948.



directed against the mucosa in this locality by the pyloric canal. It was precisely this type of ulcer which lent itself to excision and pyloroplasty; I have not since the war seen an unperforated ulcer of the anterior wall of the duodenum which could have been locally excised even had I been anxious to treat it in that way. The remarkably increased frequency of posterior wall ulcer of the duodenum cannot be explained, merely on a basis of selection, by suggesting that twenty years ago more operations were performed for duodenal ulcers with recent symptoms which are now treated by the physician. Those of my patients who have come to gastrectomy after recovery from perforation have without exception presented an anterior duodenal wall free from ulceration though perhaps adherent to omentum, but a chronic ulcer of the posterior duodenal wall. Bleeding ulcers of the duodenum are always posterior in position though they may be accompanied by an anterior wall ulcer, or the whole circumference of the duodenum may be ulcerated, as it sometimes is when bleeding and perforation occur together. One is tempted to conclude that *anterior wall ulcer of the duodenum is always acute, perforating before it can become chronic*. Care should be taken in showing the same exactitude in arguing from Illingworth's figures as he himself showed in collecting them; they concern perforation of the free wall, not chronic ulcer of the posterior wall, of the duodenum.

The incidence of peptic ulcer in certain diseased states such as uræmia and septicæmia is well known. Peptic ulcer occurs also with more specific anatomical-pathological states. It may occur during convalescence from a burn and it has been described after operations on and in the course of diseases of the hypothalamus.

In the ten years before the last war there 43,000 deaths registered from that cause in England and Wales (Morris and Titmuss, 1944).

### PATHOGENESIS

A vast amount of information, more experimental than clinical, has been gathered concerning peptic ulcer, and certainly all of it cannot be applied to all peptic ulcers in men. The peptic ulcers produced in animals by histamine injection, gastro-intestinal operations, and experiments upon the bile passages and midbrain cannot without the most careful sifting be applied to the perforating duodenal ulcer of the young hyperchlorhydric, the bleeding gastric ulcer of the worn-out old lady, the acute gastric ulcers of uræmic gastritis, and the Curling's ulcer of the child with burns. There is no more reason to seek a single cause of peptic ulcer than a single cause of ulcer of the leg. The gastric and duodenal mucosa is exposed to a dangerous environment, an environment whose danger increases as the concentration of acid in it rises, yet not all hyperchlorhydrics develop ulcer and not all achlorhydrics are free from ulceration. Nevertheless, until the precise mechanism of ulcer formation is known all facts relating to ulcer are important no matter how difficult they may be

to co-ordinate or to keep in mind simultaneously. Every operation the surgeon performs for ulcer is an experiment, even though it is a logically necessary and probably desirable experiment, and to examine his results profitably for his patient and for his art he must have a background of theoretical knowledge against which to view the effects of his work. The background is now so vast that it cannot be easily arranged as a whole, and to afford each detail its due value is almost impossible; present fashion, the blinkering habit of a particular advocacy, and the vested interest of time expended in a narrow experimental field prevent detachment and lead to the bold painting of one part only of the picture while an essential trifle may be relegated to an inconspicuous corner or overlooked.

### I. INFECTION

*Blood infection* has been suggested as a factor in the production of acute ulcer. Ulcers are common in septicæmia. Rosenow (1921) in the Mayo Clinic produced ulceration by the intravenous injection of streptococci from human ulcers and from the teeth of man, and postulated an "elective affinity" of streptococci for gastric mucosa as for certain other tissues. Most later workers have been able to produce gastro-duodenal ulceration by streptococcal inoculation only when large doses were employed and multiple infective lesions were produced elsewhere. Ivy (1920) produced similar ulcers by the injection of sterile broth and lamp-black, so perhaps the streptococci acts only as emboli in Rosenow's experiments.

*Lymphatic infection* was suggested to Braithwaite (1923) by the frequent coincidence of chronic appendicitis with peptic ulcer. He showed by dye injection that in lymphatic drainage from the ileo-cæcal angle to the superior mesenteric glands and receptaculum chyli there is some overflow into the subpyloric glands and even into the duodenal wall; some drainage occurred also along the edge of the omentum to the stomach. Braithwaite explained the location of ulcers by the numerous lymph follicles on the lesser curvature and just beyond the pylorus.

The theory that infection either produces or maintains gastro-duodenal ulceration cannot yet be discarded out of hand. When a peptic ulcer is seen at operation in an acute phase, the degree and extent of œdema in and beyond the ulcerated organ, and the considerable and obviously inflammatory enlargement of related glands is very striking and memorable. A similar degree of local œdema and as angry a regional lymphangitis in relation to an acid burn of the skin would be regarded as proof of secondary infection by a quite virulent streptococcus. The finding of Barber and Franklin (1946) of only yeasts, coliform bacilli and non-hæmolytic streptococci in the normal and hyperchlorhydric stomach, of virulent pathogens only in the achlorhydric stomach is no proof (nor was it advanced as proof) of the absence of pathogens from peptic ulcers in certain of their phases.

The presence of pathogens in peptic ulcer has been proved by numerous workers before and after Rosenow, from Böttcher (1874) to Seley and Colp (1941). Some workers have obtained positive cultures from 82 per cent. of gastric and 92 per cent. of duodenal ulcers, though most find gastric ulcers more commonly infected than duodenal, and malignant more commonly infected than simple.

## II. TOXINS

Acute peptic ulcer occurs in uræmia, diphtheria, and the sepsis which may follow burns. Bolton (1913), by injecting repeatedly into goats an emulsion of the gastric mucosa of monkeys, produced a "*gastro-toxic serum*" which, reinjected in monkeys, produced peptic ulcers in them.

## III. VASCULAR DISTURBANCE. LOCAL ANÆMIA

Endarteritis obliterans is always present in chronic ulcers, but in young men at least is probably secondary to the inflammatory process. In elderly patients with a normal or low acid and a dyspepsia of late onset, arteriosclerosis may well be important. Local mucosal anæmia certainly leads to ulcer formation; simple ligation of gastric vessels, even 80 per cent. of them, does not lead to ulceration, but extensive thrombosis in a single vessel, that produced by the intra-arterial injection of formalin for example, is productive of a chronic ulcer. Local mucosal anæmia may be produced by spasm of the stomach wall, and so also may ulceration. It has not been easy to know whether spasm or hyperchlorhydria plays the more important rôle in human duodenal ulcer, for both are usually present together. Spasm produces ulcer and ulcer produces spasm. Hyperchlorhydria provokes spasm, and hyperchlorhydria in certain circumstances produces ulcer. Pilocarpine and physostygmine have long been known to induce gastric spasm and acute ulceration. There is, however, one observation which proves that local hypermotility alone, probably by producing local mucosal ischæmia, will lead to ulceration even without hyperchlorhydria, and one observation which suggests that at least one type of "acid ulceration" is provoked not by acid destruction but by the local spasm which the acid excites. The first of these observations is that of Dodds and his associates (1934) who produced chronic ulcer with perforation by the oral and subcutaneous administration of pituitrin, which, they showed does not increase acid secretion but actually annuls the secretory effect of histamine simultaneously injected. Later workers (Byrom, 1937; Nedzel, 1938) have confirmed these experiments and have subscribed to the view that pituitrin produces local mucosal anæmia by spasm, and that the anæmic mucosa is thus rendered sensitive to gastric digestion, losing its natural protection against acid-pepsin. The second relevant observation is that of Starr and Steinberg (1934) who showed that the

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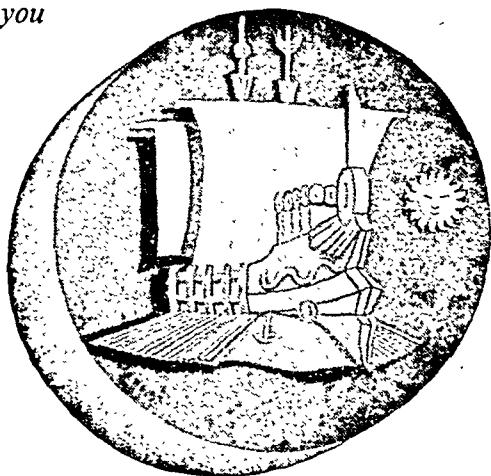
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ulceration which invariably follows exposure of an isolated jejunal loop to undiluted gastric juice can be prevented from developing by first stripping it of its muscle coat ; when the muscle coat is so stripped ulcers develop not in the stripped segment but in the segment below that still retains an intact muscle coat ; this seems to suggest that acid-pepsin ulceration of isolated jejunum is not due directly to digestion but to the effect of digestion upon the anæmic mucosa of a spastic bowel ; the acid produces spasm, and the spasm a local anæmia which permits digestion.

#### IV. TRAUMA

The mucosa of the magenstrasse is tightly bound down to the muscularis, fails to move over the muscle when solid particles pass and is, therefore, exposed to bruising. Patches of jejunal mucosa, grafted on stomach, ulcerate only if transplanted on the magenstrasse (though several explanations other than trauma might be advanced in this connection) (De Takats and Mann, Morton). There is a similar unresilient mucosa in the first part of the duodenum, but on the anterior wall, where acute ulcers are commonest, rather than the posterior, where most chronic ulcers lie. In a few clinical instances peptic ulcer has been reasonably enough ascribed to external abdominal trauma (Eusterman and Mayo, Gerendsay, Kinmonth). To establish the causal relationship the causative injury should be of a nature likely to traumatise the stomach, the resultant ulcer should be demonstrated by convincing physical signs, or at operation or autopsy, and it should be substantiated that no ulcer existed previous to the injury ; in Kinmonth's case of a boy of 15 years, an operation performed immediately after the injury displayed a rent in the mesentery, which was closed, but no abnormality of the stomach ; the ulcer was found seventeen days later in the course of an operation for hæmatemesis.

#### V. HYPERACIDITY

The most that can be said relative to the rôle of hyperacidity in ulcer-production in man, is that duodenal ulcer is more likely to occur in patients who have a high acid value in their stomach content. Hyperchlorhydria is present in 90 per cent. of duodenal ulcers, achlorhydria never, and experimentally it is easily possible to produce chronic peptic ulceration by exposing mucosa of one kind or another to a high concentration of hydrochloric acid. Injection of 0.4 per cent. hydrochloric acid, drop by drop for eight hours a day through a gastric fistula, gives a chronic lesser curve ulcer (Mann and Bollman, 1932) and pepsin given together with the hydrochloric acid hastens the appearance of the ulcer (Langenskiöld, 1913 ; Kolough, 1945). Mann and Williamson (1923) showed that if the duodenal content were diverted to the ileum and the jejunum exposed to undiluted gastric juice, a typical chronic peptic ulcer of the jejunum developed

almost invariably. The drug cinchophen induces gastric hypersecretion and the formation of a chronic peptic ulcer, usually in the stomach but sometimes in the duodenum, whose appearance is accelerated but whose rate of healing is unaffected, by the simultaneous ingestion of bone (Van Wagoner and Churchill, 1932; Stalker, Bollman and Mann, 1937). Similarly, the hyperacidity which follows injection of histamine may be employed to produce artificial ulcers by injecting that drug subcutaneously in beeswax (Code and Varco, 1940), though it is not suggested that histamine, or cinchophen for that matter, or even the mechanism by which they increase acid secretion, is in any way related to peptic ulcer in man.

## VI. FAILURE OF NEUTRALISATION OF ACID. GASTRIC SELF-PROTECTION

There is an old observation, whose source I cannot remember and whose truth I have never tried, for it does not greatly strain my credulity, that a living arm can be immersed indefinitely in gastric content without harm, while an amputated limb suffers immediate digestion. It is certainly true that post-mortem digestion of the gastric mucosa quickly follows the cessation of circulation and death of that mucosa. The reason for the happy failure of normal gastric content to digest normal gastric mucosa, and even for the failure of hyperacid gastric juice to digest the great bulk of the gastric mucosa with which it comes in contact, is no more known than the mechanism by which so strong an acid as hydrochloric is secreted at all. At least two equally satisfactory but mutually exclusive theories of acid secretion have been produced (Conway, Fitzgerald and Walls, 1945; Bull and Gray, 1945) in the second century that has followed the detection by Prout (1831) of hydrochloric acid in the gastric juice, and many more explanations, equally unproved, have been advanced for the self-protection against acid-pepsin which all but the most inconsiderable fraction of the total area of human mucosa seem to enjoy. If all the human gastric mucosa available to-day were laid cut edge to cut edge without stretching, it would serve as a complete velvet carpet for the County of London, yet I doubt if all the peptic ulcers in the world would cover a much greater area than my desk. Even in the stomach, the seat of peptic ulceration, all but a fraction of one per cent. of its mucosa remains unharmed, however potent the gastric juice to which it is exposed.

It may be that the mucosal cells of the normal stomach resist acid digestion because, alkaline themselves, they are bathed on five sides by alkaline fluid and protected on the sixth by a lipoid membrane. It may be that a film of mucinous material lies like a protective film on the mucosal surface. It may be that the cells of the gastric mucosa contain an "anti-pepsin" such as can be extracted from the heads of tapeworms and such as Morrison (1945) has tried to obtain from the human and the frog stomach and to use in the treatment of peptic

ulcer. Certain it is that in the normal human stomach acid is neutralised, buffered, and diluted by food, mucin, and perhaps by regurgitating duodenal content, while acid passing into the duodenum is buffered by bile and pancreatic and duodenal juices (Bennett, 1921; Babkin, 1944). Partial pyloric obstruction, if it prevents the regurgitation of duodenal juice, prevents the healing of artificial gastric ulcers though it does not excite ulceration (Hughson, 1927). The diversion of bile (Hooper and Whipple, 1916; Kapsinow, 1926; Berg and Jobling, 1930) and the exclusion of pancreatic juice from the duodenum (Ivy, 1920; Elman, 1928; Elman and Hartman, 1931; Elman and McCaughan, 1927; Matthews and Dragstedt, 1932) are equally likely, though not certain, to lead to duodenal ulceration. The degree of dilution and buffering of acid gastric content probably varies from one part of the stomach to another and buffering is certainly different in degree and in kind in the various parts of the stomach, in the duodenal bulb, and in the remainder of the duodenum. Buffering is probably fairly rapid and complete in the gastric sump of the dependent greater curvature (which is the only part of the stomach whose content we measure by test meal), much less complete on the surface of the lesser curvature, and entirely immeasurable by contemporary methods in the duodenal bulb (Daintree Johnson, 1948). In the self-protection which the gastric mucosa normally manifests, and singular freedom from general ulceration which the gastric mucosa enjoys even in hyperchlorhydric patients who develop ulcers, lies the key to the ulcer problem. Local differences in the effectiveness and rate of buffering may well be the explanation of the uniform siting of peptic ulcers in the first part of the duodenum and on the magenstrasse.

## VII. THE ULCER DIATHESSES

Hurst (1924) enunciated a hypothesis of the general diathesis of tissues and of the local diathesis of organs, and his general argument has a high validity. Duodenal ulcer is predominantly a disease of hypersthenic, anxious, emotional, sensitive, hard-working men with small hypermotile, steerhorn stomach which empties early, and after emptying, continues to secrete acid even, or perhaps particularly, during sleep. The "gastric ulcer diathesis" is less characteristic but is typified by the listless, feeble patient who has a long J-shaped stomach and perhaps tension on the lesser curvature which lies high above the buffered sump.

## VIII. NERVOUS INFLUENCES

The muscle spasm and hyperacidity of ulcer patients are definitely and notoriously dependent on psychological influences. The "duodenal ulcer diathesis" has already been considered and it is common knowledge even among the laity that the duodenal ulcer is "left at the office stool"; that the bank manager's dyspepsia is greatest at the



time of his annual balance and that his health improves on holiday. There is available now evidence that nervous influences, initiated below the psychological plane, may produce peptic ulceration. Rokitsky (1841-46) a hundred years ago made the observation that disintegration of gastric and œsophageal mucosa (gastromalacia) occurred sooner after death, and perhaps before death, in patients suffering from certain intracranial diseases. Beattie (1932) produced hæmorrhage, erosion, and even perforation of stomach and duodenum by damage to or stimulation of the hypothalamic region, where vegetative centres are situated, and his work has been confirmed (Watts and Fulton, 1935; Manning, Hall and Banting, 1937). These modern experiments substantiate the brilliant early experimental work of Schiff (1854), Brown-Sequard (1876), Ebstein (1874), and Mogilnitzky and Burdenko (1926) in the same field. On a more peripheral plane, peptic ulceration has been produced by electrical stimulation of the vagi in the thorax and the abdomen (Stahnke, 1924; Keppich, 1921), and by the continuous administration of acetylcholine (Neches, 1937). The whole body of clinical and experimental evidence of the relation to peptic ulceration of organic disease of the central nervous system has been collected and weighed by Cushing (1932) in his classical paper. Cushing concludes that not only may physical stimulation of para-sympathetic pathways in the posterior hypothalamus, brainstem, vagus trunks and vagus nerve ends lead to hypersecretion, hyperchlorhydria, hypermotility, hypertonicity (especially of the pyloric region), mucosal ischæmia, and ulceration, but that psychical influences governing the vegetative centre in the hypothalamus may have an identical effect. Cushing's work thus co-ordinates local causes of ulcer, hyperchlorhydria, hypertonicity, and ischæmia, with the psychological implication of Hurst's diatheses. Even the common anatomical situation of peptic ulcers have been related to this neurogenic scheme, for Babkin (1938) reports that vagal nerve ends are most numerous, and local hypermotility therefore probably maximal, on the lesser curvature and in the duodenal bulb.

#### IX. DIETETIC, RACIAL, AND ENVIRONMENTAL INFLUENCES

That either a dietetic or a racial factor or both is important in the genesis of ulcer is implicit in the observation of McCarrison (1944) that the incidence of peptic ulcer is 58 times commoner in South India than in North India. Tobacco has been blamed for the hypersecretion which precedes ulcer, but if tobacco were important, duodenal ulcer incidence would have climbed in women during the last thirty years; the chief increase in duodenal ulcer over that period has been in males; chain-smoking may be a manifestation merely of the psychological pattern which happens also to be associated with ulcer.

Peptic ulcers are common in animals kept short of vitamin C; patients with peptic ulceration can sometimes be shown to have a high tolerance for intravenous ascorbic acid and to have also a high

capillary fragility. Deficiency of vitamin A has also been blamed. Peptic ulceration increased in frequency in central European cities during the lean years of the period between the wars, but the increase was in gastric not in duodenal ulcers. It is doubtful whether nutritional influences are of any importance in the genesis of duodenal ulcer.

### SUMMARY

To summarise shortly so many facts, observations, and experiments is to sacrifice accuracy to brevity, but the following conclusions may reasonably be drawn :—

1. Duodenal ulcer is more likely to occur in hyperchlorhydric than in normal subjects ; it does not affect the achlorhydric patient.
2. A normal or strongly acid gastric content *and* hypermotility are probably both necessary for the production of a duodenal ulcer.
3. Hyperacidity and hypermotility may both be produced by central nervous influences operating probably through vagal channels.
4. Gastric ulceration probably differs in its genesis from duodenal ulceration. It occurs in a different type of individual, and it may occur in a hyperchlorhydric or apparently achlorhydric stomach.
5. The almost universal location of peptic ulceration either on the lesser curvature or in the first part of the duodenum, and the apparent immunity of the remainder of the mucosa even of the hyperchlorhydric stomach must be explicable by local peculiarities of mechanics, motility, cellular protection, or chemical buffering which are not at present understood. It is significant that ulceration is commonest not in a mucosa which secretes a high concentration of acid, but in such adjacent mucosa as that of lesser curvature, duodenum, jejunum (after gastro-jejunostomy), œsophagus (in short œsophagus and in relation to heterotopic oxyntic cells), and ileal mucosa adjacent to heterotopic gastric epithelium in a Meckel's diverticulum.
6. Lastly it should be added that the hypersecretion, and presumably the hypermotility, which seems to be related to the genesis of duodenal ulcer is not the hormone-induced response to food, but the nocturnal vagal overaction during sleep, which is reflected by the high night secretion of duodenal ulcer subjects, and the hypersensitivity of the parasympathetic centres to hypoglycæmia, which is reflected sometimes in the curve of the insulin test meal.

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## PRIMARY THORACOPLASTY

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PRIMARY thoracoplasty has been defined by Max Pinner (1945), amongst others, as "a thoracoplasty operation which is not preceded by pneumothorax attempts." My talk this evening is based upon a review of cases of primary thoracoplasty which have passed through my hands in the last four years, and my reason for the choice of this subject is the fact that recently we have been tending to resort more frequently to thoracoplasty as our first line of attack. As a physician I am not proposing to concern myself with questions of surgical technique or management but will confine my remarks to the consideration of those factors which led to the choice of thoracoplasty in preference to other forms of collapse. I have chosen the past four years because prior to 1944 primary thoracoplasty was a comparative rarity. Its theoretical advantages in patients with extensive fibro-cavernous lesions had been conceded by Davies (1933) and Archibald (1925), but there was a considerable hesitancy about translating theory into practice; and as late as 1937 such an authority as John Alexander had committed himself to the statement that pneumothorax should, almost without exception, be attempted before performing thoracoplasty. It was unfortunate that many physicians, sharing with their patients a sense of relief at the postponement of a major operation, continued to overlook the proviso inserted by Alexander that an inadequate pneumothorax should be promptly abandoned. Having climbed upon the A.P. band wagon they clung there tenaciously, concentrating upon the short-term results of pneumothorax, which were reasonably good, and regarding the complications as unavoidable concomitants of an otherwise admirable method. Long-term sequelæ such as an unexpandable lung hardly entered into the picture at all. The answer was so simple—a permanent pneumothorax—an answer which disregarded completely one of the fundamental concepts of pneumothorax, that it was a reversible procedure.

In 1944, however, we were brought sharply face-to-face with reality when Rafferty produced his monograph on *Artificial Pneumothorax*, a piece of work for which those of us who treat respiratory tuberculosis should be forever grateful. Here were facts which could not be ignored, and arguments, backed by reason and evidence, compelling a reorientation of ideas and the elimination of certain groups of cases from the pneumothorax list. The flight from pneumothorax had begun, and almost overnight primary thoracoplasty moved

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from the realms of theory into those of fact. We had to realise that there were certain groups of cases requiring major collapse therapy in which pneumothorax was contraindicated. It became the chest physician's duty to recognise these cases and to refrain from aggravating the disability by wanton violation of the pleural cavity.

Before proceeding to consider in more detail the factors which influence choice of therapy it is necessary to formulate one or two principles which must remain fundamental to our thesis. Pneumothorax is a temporary and reversible form of collapse and should not be used when the nature and distribution of the lung lesion suggests that nothing short of permanent collapse will be adequate. When there is good reason to suppose that the course of pneumothorax will be marred by complications this constitutes a valid argument in favour of thoracoplasty in those cases in which major collapse is required. If we accept these principles then the situation is clarified considerably and for certain groups of cases primary thoracoplasty becomes an automatic first choice when collapse therapy is considered. These groups comprise (1) cases showing extensive fibro-caseous disease, (2) cases with large apical cavities, and (3) cases with active tuberculous disease of a major bronchus. In the first group the main argument against pneumothorax lies in the extent of the disease and the certainty that, even in the event of pneumothorax being initially successful, healing will be accompanied by fibrous change and lung shrinkage of such a degree that either re-expansion will fail to take place or will take place only at the expense of mediastinal shift and over-distension of the opposite lung. Should one decide to accept the displacement of the mediastinum and the over-distension, is the heavily scarred and relatively functionless lung worth the price? I think most of us will agree now that primary thoracoplasty is the answer in these cases, especially when we reckon in also the high incidence of extensive pleural adhesions and accompanying effusion. Similar arguments hold good in the second group, those showing large apical cavities. Here the emphasis is perhaps more on the possible pleural complications, which we know to be high. Apical cavities of any degree are usually surrounded by adhesions and require separation not only from the lateral chest wall but usually also from the thoracic dome and the mediastinum. Even in the most skilled hands I regard this as a hazardous procedure, and a large percentage of these cases develop effusion. The effusion may not be an empyema, but I feel that in the past we have not taken sufficient account of the damage to function done by even a simple effusion. It has required the bronchspirometric researches of Pinner and his colleagues to bring this home to us and to cause us to view with dissatisfaction a treatment which, while controlling the diseased portion of the organ, produces a complication which leads to considerable functional impairment of the organ as a whole. Furthermore, as in the first group of cases, many of these apical cavities are lesions which, because of their extent and the

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associated degree of destruction, require permanent collapse, and I have now no hesitation in electing to treat them by primary thoracoplasty.

The presence of active tuberculous disease in a major bronchus brings a host of complications in addition to the problem of the disease in the lung parenchyma. The bronchial lesion by itself leads to interference with bronchial drainage, to atelectasis, to spread of the tuberculous disease and occasionally to pyogenic infection and to bronchiectasis. A pneumothorax done in the presence of such a bronchial lesion will merely aggravate and hasten the onset of these complications and in addition will expose the patient to a high incidence of empyema. If he survives those risks his ultimate reward will almost certainly be a completely unexpandable lung. In the pre-streptomycin era primary thoracoplasty was accepted as the method of choice in these cases, when collapse was required for the lung lesion. I doubt very much if even the known specific effect of streptomycin on bronchial disease has altered the picture to any extent. Healing of the bronchial lesion under the influence of the antibiotic can and does occur, but unless the ulceration has been very superficial and limited in extent stenosis of the bronchus results, and the combination of stenosis and pneumothorax adds up to one result—unexpandable lung. If permanent collapse is bound to ensue then it should be produced by a permanent method, and where collapse therapy is required I still consider tuberculous ulceration of a major bronchus to be an absolute indication for primary thoracoplasty.

In the three groups which we have already considered the case for primary thoracoplasty is a strong one, and I do not think that there can be any very active disagreement on the subject. There are, however, one or two other groups in which I feel that thoracoplasty should be our method of choice but to which I am prepared to find a certain amount of opposition. The first of these comprises cases in which there is a definite history of pleural effusion. I have found myself at variance from time to time with some of my colleagues who maintain that pneumothorax in these cases is always worth a trial. Perhaps I have been unfortunate, but my experience has been that in such cases, while occasionally a pneumothorax space may be obtained, adhesion formation is so extensive that a really effective pneumothorax is a complete rarity and that a tentative trial of this method results only in a waste of time. Consequently I have now made it a practice to treat all these cases by primary thoracoplasty, and so far I have had no reason to be dissatisfied with the results. I believe that even a relatively limited lung lesion in such cases is best treated by thoracoplasty, particularly when it occurs in a young man who has his career in front of him and who can ill afford to risk a further breakdown at perhaps a critical period in his fortunes. These patients are good surgical risks and the gain to them of a successful operation, measured in terms of future security and health, is enormous and,



in my view, well worth while. I agree that the temptation to delay operation may be considerable—there is still a tendency to regard thoracoplasty as a drastic procedure—but delay in so many instances means a missed opportunity and the eventual performance of a more extensive operation in much less advantageous circumstances.

There is one other type of case in which I find myself veering more and more towards thoracoplasty as the procedure of choice, and that is the case with a relatively limited fibrotic lesion situated at the extreme apex of the lung. Here a primary thoracoplasty appears to me a completely logical method of treatment. Extreme apical lesions do not usually respond well to pneumothorax. One may free them from the dome by pneumolysis only to find them firmly plastered on to the mediastinum, and, presented with this somewhat unsatisfactory type of collapse, one exposes the patient over a period of years to the possible complications of pneumothorax, being fortunate if in the end one escapes with only a minor degree of pleural thickening. A very limited thoracoplasty at the beginning will suffice to control the diseased area permanently and effectively without fear of late complications or functional disability. The same argument applies, I think, in a somewhat similar type of case, the man in his twenties or early thirties, in good general condition and with relatively little in the way of symptoms. On an ordinary skiagram he has a limited lesion in the upper zone which appears hard and stable. A tomogram, however, shows a small central cavity, and his sputum inoculated into a guinea-pig gives a positive result. Such a lesion, secreting tubercle bacilli, demands collapse, and I believe that for a limited fibrotic area permanent collapse by thoracoplasty is always preferable. In cases such as these last two I am influenced to a certain extent in my preference for thoracoplasty by what is best described as the "age and wage" factor. A limited lesion with a degree of fibrosis postulates a reasonable resistance on the part of the patient, leading to the assumption that if that lesion can be given the mechanical assistance of collapse there is every hope that it will be permanently and effectively controlled. For a man in the 20-30 age group, in other words at the time of life when he is battling to get himself established and to make his career, permanent effective control represents a highly desirable goal. He has his life to live, his work to do, his wage packet to earn, and he desires to devote himself to these pursuits with a mind as free from worry as possible. If we elect to place our bet on his resistance to the disease and decide to leave it to nature and his own ability to modify his mode of life we may get away with it. We have, however, made him feel that he is not as other men are, we have sown the seed of doubt and fear in his mind and ever at his shoulder is the bogey of a "spread" and a breakdown. If we collapse the lung by any method we have done something to remove the bogey, but if pneumothorax is the method chosen we impose upon him the necessity for regular attendance at the clinic

for his refills, the possibility of complications and the ever-present query, "Will it be all right when the refills stop?" We all know how many of these patients tend to cling to their A.P.'s and we know, too, the indecision with which we ourselves are afflicted when the question of termination of treatment arises. During these years, also, the patient has been unable to escape from the atmosphere of tubercle, his fortnightly visit reminds him of his disability and he becomes tuberculosis-conscious. I cannot believe that this is good for the type of case which we have in mind. Taking these points into consideration I believe that it is reasonable to consider the "age and wage" factor in deciding on treatment and that primary thoracoplasty has more to offer such a patient than pneumothorax. He has his operation, followed by an adequate period of sanatorium treatment, and then he may be allowed to take up his normal life once more, with the assurance that the diseased area is permanently controlled and that, apart from folly on his part, he should remain well. It may be said that it is unreasonable to subject a man to a mutilating operation which might not after all be necessary. I cannot agree that a limited thoracoplasty is a mutilating procedure. It entails what the word "thoracoplasty" itself implies—a remoulding of the chest wall over the diseased area. If we wait until we have to operate for a totally destroyed lung or to obliterate pyopneumothorax then perhaps we can refer to mutilation, but I do not think that a limited readjustment of the thoracic contours merits such a description.

Descending for a moment from theory to fact, I have reviewed my cases during the past four years and I find that in 30 patients we decided upon primary thoracoplasty as the treatment of choice. In only one instance was operation declined, a percentage which, I think, reflects great credit upon the intelligence of the patients involved. Several of them have explained to me their ready acceptance of the idea of operation by saying that they watch closely the readmissions and have noted that the thoracoplasty cases do not have to return! In the 30 cases quoted all the groups which I have mentioned are represented. Six had previous pleural effusions and were submitted to thoracoplasty without further ado. Fifteen had fibro-caseous disease of such an extent that pneumothorax was not even considered, while four had large apical cavities. Three had either limited apical or upper zone lesions and were dealt with under the "age and wage" rule, while two had definite tracheo-bronchial disease.

I realise, of course, that one cannot make the arguments which have been advanced completely cast-iron without a long-term follow-up, and in tuberculosis I doubt if anything less than a ten year period is completely convincing. We shall, therefore, be rounding off our discussion sometime about 1958! We have, however, ample evidence of the durability and effectiveness of thoracoplasties other than primary, and with that evidence as a guide I feel that we can recommend primary thoracoplasty to our patients with confidence. In the 30 cases which

I have mentioned neither the patients nor I have had any reason so far, either in the immediate post-operative phase or later, to regret our choice.

In a conversation a short time ago with some medical colleagues I heard a regret expressed on the present tendency to regard the treatment of pulmonary tuberculosis as almost entirely a surgical problem. The remark was intended seriously, which made it all the more deplorable in view of its inherent fallacy. In the first place I can see no possibility whatsoever of the treatment becoming entirely a surgical problem. It is, and is likely to remain, predominantly a medical one, but we should be failing lamentably in our duty to the patient if we did not take advantage of the advances made in the sister art of surgery. The thoracic surgeon is not a rival—he is a man and a brother and has shown himself to be such over the years. He has had to content himself for long enough with the crumbs which fell from the rich man's table, with the failures of medical treatment, with the tattered and cavity-riddled lungs, the empyemata, the broncho-pleural fistulæ—and with these he proved himself. I do not think that we need hesitate now to ask him to do a primary thoracoplasty: the main beneficiary of our action will be the patient.

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## CLUBBING OF THE FINGERS

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HIPPOCRATES in the fifth century B.C. described curving of the finger nails for the first time in a case of empyæma. Even to-day the French refer to clubbing of the fingers as *doigts hippocratiques*. According to Ebstein, Hippocrates confined his attention only to the increased curvature of the nails. It was Caelius Aurelianus who first drew attention to the drum stick or clubbed appearance of the digits.

There seems to have been no further mention of this phenomenon until 1832 when Pigeaux described finger clubbing in cases of pulmonary tuberculosis. Thereafter it was recognised as a definite clinical entity. Von Bamberger in 1889 reported the condition in certain diseases of the heart and lungs and in 1891 presented a classical description of this phenomenon. In 1890 Marie distinguished finger clubbing from acromegaly with which it had been confused by Erb and Fraentzel.

Clubbing of the fingers and toes may be defined as a uniform painless enlargement of the ends of the fingers or toes. Hypertrophic osteoarthropathy is a more severe degree of this process and involves the more proximal parts of the extremities, it may also be painful.

Mendlowitz has classified clubbing into three main groups :—

- I. Symmetrical—involving all the fingers and toes.
- II. Unilateral—involving the fingers or toes of one hand or foot.
- III. Unidigital—involving only one finger.

Hypertrophic osteoarthropathy may occur as a feature of any of these varieties of clubbing.

### I. SYMMETRICAL CLUBBING

This may be divided into acquired and hereditary and the acquired further subdivided into pulmonary, cardiac, gastro-intestinal, hepatic and a miscellaneous group.

#### (a) *Acquired Symmetrical Clubbing*

PULMONARY.—Clubbing of the fingers may occur in many types of respiratory disease. It is seen most frequently in chronic suppurative conditions of the lungs.

(1) *Empyæma*.—In 30 patients suffering from empyæma clubbing of the fingers was present in every case. In this series 18 of the patients developed an empyæma during or following lobar pneumonia. The onset of the empyæma in these cases was accompanied by early finger clubbing. The remaining 12 patients developed an empyæma as a

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complication of lung abscess, bronchiectasis or bronchial carcinoma. This condition had been present for several weeks and every patient showed marked clubbing of the fingers.

(2) *Bronchiectasis*.—Of 30 patients with bronchiectasis 24 showed clubbing of the fingers, 80 per cent. In 5 of these cases the condition was very marked, 18 per cent. of the total.

(3) *Lung Abscess*.—In 12 cases of lung abscess, finger clubbing was demonstrated in every case, 100 per cent. In 7 of these, 58·3 per cent., the clubbing could be described as gross.

(4) *Bronchial Carcinoma*.—Clubbing of the fingers may be present in many cases of bronchial carcinoma, or, indeed, in most cases of intra-thoracic tumour, 54 out of 60 cases of bronchial carcinoma, 90 per cent., showed finger clubbing and in 4 of them the clubbing was very marked. Duncan quotes a case of bronchial carcinoma which developed gross hypertrophic osteo-arthritis and Ayre described marked finger clubbing in a patient in which the clubbing of the soft tissues, hypertrophy of the distal portions of the extremities and the characteristic changes in the long bones became evident within a period of one month. Finger clubbing may be the earliest and first sign of bronchial carcinoma, and Craig quoted such cases where clubbing of the digits had been misdiagnosed as rheumatoid arthritis and acromegaly.

Finger clubbing may be demonstrated also in some cases of pulmonary metastasis. One patient, a boy, suffering from osteogenic sarcoma of the tibia had widespread metastasis in the lungs and showed early clubbing of the fingers. Finger clubbing was seen in a woman with a carcinoma of the cervix who had multiple secondary tumour deposits in the lungs. Kruger described this condition in pulmonary metastasis from a carcinoma of the breast while Renander discussed hypertrophic osteo-arthritis in metastases in the lung from a tumour of the adrenal.

(5) *Pulmonary Tuberculosis*.—Digital clubbing is observed less frequently in cases of pulmonary tuberculosis but may be present, according to Trousseau, in the long-standing cases. Fishberg found that whenever clubbed fingers occurred in phthisis the patient was also suffering from dyspnoea and dilatation of the right side of the heart. Mendlowitz, however, has seen clubbing develop in as short a time as three months in a case of pulmonary tuberculosis with symptoms of activity for only six months. In 60 patients in this series, who were suffering from pulmonary tuberculosis clubbing of the fingers was present in only 4 of them, 6·6 per cent., and all were cases of long standing.

(6) *Fibrosis of the Lung*.—Finger clubbing may be seen in conditions producing fibrosis of the lung such as pneumokoniosis, unresolved pneumonia and atelectasis. In 5 cases of silicosis in which no complication could be detected clinically, radiologically or bacteriologically no finger clubbing was present. In 10 cases of silicosis

complicated by pulmonary tuberculosis clubbing was evident in 4 of them and in 5 patients with silicosis and bronchiectasis clubbing was present in each case. Out of 6 patients with unresolved pneumonia and 10 with atelectasis symmetrical clubbing of the fingers had developed in 2 and 4 cases respectively at the end of a month.

(7) *Emphysema*.—Finger clubbing may be seen in patients with emphysema. In this disease, however, the clubbing is usually associated with some underlying pulmonary infection such as bronchitis or bronchiectasis. Of 100 patients with emphysema digital clubbing was present in 22 per cent., 15 of these cases were associated with bronchiectasis.

(8) *Thoracic Deformities*.—Clubbing of the fingers may be associated with deformity of the chest. Von Bogaert and Herman described clubbing in cases of Pott's disease and Stephan drew attention to finger clubbing present in patients with chest deformities produced by rickets. It is well known, however, that empyæma may in time produce such thoracic deformities as kyphoscoliosis and therefore in some cases it may be difficult to determine the primary cause of the finger clubbing.

(9) *Pulmonary Endarteritis*.—Rothschild and Goldbloom reported a case of obliterating pulmonary arteritis with cyanosis and intense dyspnœa but in which no clubbing of the fingers developed. Clubbing of the digits was present, however, in 3 cases of advanced congestive failure due to mitral stenosis in which, at post mortem, gross atheroma and sclerosis of the pulmonary vessels was seen.

(10) *Actinomycosis and Syphilis of the Lung*.—Wynn reported clubbing of the fingers in a case of actinomycosis, and Smirnoff described finger clubbing in congenital syphilis. Cases of acquired syphilis affecting the lungs and in which clubbing of the fingers was a feature have been described by Munro, Pye-Smith and Schmidt.

It would thus appear that clubbing of the fingers and toes may occur in a variety of conditions associated with anoxæmia or pulmonary sepsis.

**CARDIAC.**—(1) *Congenital Heart Disease*.—Clubbing occurs to a marked degree in congenital heart disease. It is very common in the cyanotic group of congenital cardiac disease and is not seen in the acyanotic group unless complicated by subacute bacterial endocarditis or bronchiectasis. In 10 cases of congenital heart disease in which there was a venous arterial shunt clubbing of the fingers and toes was present in all the patients. The condition was seen in 4 cases of patent ductus arteriosus which were complicated by bacterial endarteritis.

(2) *Subacute Bacterial Endocarditis*.—Finger clubbing was demonstrated in 20 out of 22 cases of subacute endocarditis, 99 per cent. Wámoschr stated that clubbing is rarely seen in the bacteria-free stage of subacute bacterial endocarditis although in the cases quoted above the clubbing remained throughout the illness, and, in 3 patients treated with penicillin and apparently cured, was present to a slight degree a month later.

(3) *Rheumatic Endocarditis*.—Clubbing of the fingers may be present in patients suffering from pure rheumatic endocarditis in whom no evidence of subacute bacterial endocarditis could be detected at post mortem. In 10 such cases of uncomplicated chronic active rheumatic endocarditis digital clubbing was found in 5 of them, 50 per cent.

(4) *Congestive Cardiac Failure*.—Davidson and Bullowa have described clubbing in cases of congestive cardiac failure. The usual cause of this cardiac failure according to Findland and Sutliff *et al.* is mitral stenosis. In these cases therefore the primary cause of the clubbing may be pulmonary due to an associated atherosclerosis of the pulmonary vessels.

Clubbing of the fingers can be demonstrated therefore in the cyanotic group of congenital heart disease, in subacute bacterial and rheumatic endocarditis and in congestive cardiac failure although pulmonary factors may play a part in this latter case.

GASTRO-INTESTINAL DISEASE.—Clubbing of the fingers may be encountered in many types of gastro-intestinal disease.

(1) *Carcinoma of the Œsophagus*.—Hirschfeld referred to clubbing of the fingers in a case of œsophageal carcinoma and this case was quoted by Janeway in 1903 in his review of the causes of hypertrophic osteo-arthritis.

(2) *Pyloric Stenosis*.—Clubbing of the fingers may be associated with pyloric stenosis. Such a case was described by Denning in 1902 and quoted by Shaw in Allbut's *System of Medicine*.

(3) *Tuberculous Enteritis and Regional Ileitis*.—Mendlowitz has observed clubbing of the fingers in cases of intestinal tuberculosis and in regional ileitis. The only cases of finger clubbing associated with tuberculous enteritis in this series were present in 3 patients with advanced open pulmonary tuberculosis. It is difficult in these cases to determine whether the changes in the fingers were due to the enteritis or to the pulmonary condition.

(4) *Chronic Dysenteries*.—Brulé *et al.* and Lemierre and Lévesque describe clubbing of the fingers in cases of chronic amœbiasis and Mendlowitz discusses this enlargement of the digits in cases of chronic bacillary dysentery. One patient in this series who had marked finger clubbing gave a history of both amœbic and bacillary dysentery and was found to be suffering from chronic amœbiasis.

(5) *Chronic Non-Specific Ulcerative Colitis*.—Of 10 cases of ulcerative colitis in this series 2 were found to have clubbing of the fingers. This condition had been demonstrated in ulcerative colitis by Moulonquet and Salomon in 1932 and by Schlicke and Barga in 1940.

(6) *Polyposis of the Colon*.—Polyposis of the colon is a known complication of ulcerative colitis and it is therefore not surprising that clubbed fingers had also been noted in this condition. Again most of the cases have been described by French investigators notably Bensaude, Hillemand and Augier, and Brulé and Lièvre.

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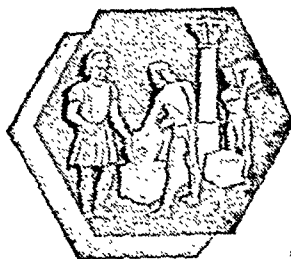
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(7) *Malignant Disease of the Alimentary Canal*.—Clubbed fingers were observed in a man of 32 years who had severe diarrhoea and was suffering from lymphosarcoma of the small intestine. Mendlowitz has described finger clubbing in cases of Hodgkin's disease of the small intestine and in carcinoma of the colon.

(8) *Sprue Syndrome*.—Fanconi noted clubbing of the fingers in some of his young children who were suffering from idiopathic steatorrhoea. Bennet *et al.* found curving of the nails and finger clubbing in 6 out of 15 cases of steatorrhoea.

In 2 cases of non-tropical sprue seen by the author digital clubbing was a noticeable feature. The clubbing was symmetrical and involved the fingers and toes.

It would thus seem that clubbing of the fingers occurs in association with those diseases of the alimentary canal characterised by chronic diarrhoea.

HEPATIC.—Clubbing of the fingers has been found in some types of liver disease.

(1) *Hypertrophic Biliary Cirrhosis*.—This condition may be characterised by clubbing which was seen in the one case of biliary cirrhosis in this series. It has been recorded by Gilbert and Fournier, Obermayer, Parmentier, *et al.*, and Rolleston and McNee in association with biliary cirrhosis. The latter authors state it is rare in cases of portal cirrhosis.

(2) *Amœbic Hepatitis and Amœbic Abscess*.—Clubbing has been observed in amœbic hepatitis and amœbic abscess but may have been due to the chronic intestinal infection present rather than the liver disease.

MISCELLANEOUS.—Symmetrical clubbing has been described in numerous apparently unassociated conditions.

(1) *Enterogenous Cyanosis*.—Stokvis, Van den Burgh and Grutterink noted finger clubbing as a feature of enterogenous cyanosis. In these cases, however, there was an associated colitis which may have produced the clubbing.

(2) *Following Thyroidectomy*.—Cushing quotes a case of a 38 year old man who developed clubbing of the fingers following thyroidectomy.

(3) *Purpura*.—Mangelsdorf described a case of purpura rheumatica in which clubbed fingers was a noticeable feature.

(4) *Polycythæmia Vera*.—Clubbing of the fingers has been described in cases of polycythæmia vera. Parkes Weber in his monograph pointed out the constant association of a high red cell count with chronic toxæmia such as tuberculosis, syphilis and malaria, conditions in which he stated that clubbing is a well-known phenomenon.

(5) *Syringomyelia*.—It is well known that syringomyelia is associated with enlargement of the hands and fingers resulting in Morvan's disease. Definite finger clubbing, however, has been described in cases of syringomyelia by Bouchard and Singer.

(6) *Vascular Diseases*.—Clubbing of the fingers has been seen in Raynaud's disease, scleroderma and acrocyanosis. In these conditions, however, changes in the lungs may occur as part of the primary disease. The finger clubbing therefore may be associated more with pulmonary than with the local peripheral lesions.

(7) *Chronic Septic Conditions*.—Moizard quoted a case, first described by Marfan, in which clubbing of the fingers was noted in a patient with chronic pyelocystitis. Well-marked clubbing rapidly developed in a case in this series of a girl, aged 16 years, who had osteomyelitis of the femur.

### (b) *Hereditary Clubbing of the Fingers*

Finger clubbing of an idiopathic type and unknown ætiology occur in certain families and have been described by Freund, Campbell and Sacosa. Friedreich reported generalised hyperostosis of the entire skeleton in 2 brothers. This condition started in the second decade without any preceding or accompanying disease. It has been suggested the condition was related to puberty and to the changes in metabolism that occur at this critical period of life.

## II. UNILATERAL CLUBBING

This condition is encountered in association with local lesions of the arm, axilla and thoracic outlet.

(1) *Aneurysms*.—The most common cause of unilateral clubbing is an aneurysm of the subclavian or innominate arteries or of the aortic arch with involvement of the former by the aneurysmal dilatation. Regnault has described clubbing of the fingers in a case of arterio-venous aneurysm of the brachial artery. In 4 cases of aneurysm of the aortic arch in this series unilateral clubbing was present in two of them.

(2) *Nerve Pressure*.—Carcinoma of the apex of the lung, described by Pancoast may involve the sympathetic ganglia on that side and produce unilateral clubbing. In a similar manner fibrotic apical lung lesions may, by pressure or traction on the nerves of the brachial plexus produce clubbing of the fingers on that side.

(3) *Costo-clavicular Syndrome*.—It is well known that aneurysms of the subclavian artery may result from the many conditions producing this syndrome. Although clubbing of the fingers has not been described in association with this condition it is very likely that mild and early clubbing may be present in these cases.

## III. UNIDIGITAL CLUBBING

This condition is very rare. In 1865 Ogle described a case of clubbing of one finger following an injury to the arm which damaged the median nerve. Lebreton in 1936 discussed unidigital clubbing in Boeck's sarcoidosis, in gout and following local trauma to the finger. Cases of unidigital clubbing are very seldom seen, however, in clinical medicine.

## LOCAL PATHOLOGICAL CHANGES IN FINGER CLUBBING

Clubbing is characterised by an increase in the amount of fibro-elastic tissue of the nail bed and of the fibro-fatty tissue of the pulp of the finger. Singer and Quirno have found dilatation and thickening of the walls of the vessels in the finger tip together with the formation of new capillaries. Parkes Weber has described an increased thickness of the periosteum of the phalanges in these cases. When the clubbing is gross actual atrophy of the bone may occur. Later new bone formation develops, especially in the region of the distal epiphysis and at the points of muscle and tendon attachments. When hypertrophic osteo-arthropathy is present an irregular growth of periosteum develops along the shafts of the bones and at the same time osteoporosis of the cancellous portion of the affected bones occurs. Thorburn observed thickening of the articular capsule and synovial membrane in the related joints and Stechemacher found small effusions in these joints. Microscopically the periosteum is thickened and Crump has described lymphocytic infiltration together with vaso dilatation, oedema and even small hæmorrhages into this tissue. There is also a generalised osteoclastic activity with osteoporosis of the affected bone and separation and thinning of the trabeculæ with disruption of the Haversian System.

## CLINICAL FEATURES OF FINGER CLUBBING

Clubbing of the fingers is seen most commonly in men although there is no true sex distribution of this phenomenon. The sex incidence depends entirely on that of the underlying condition. In this series the sex ratio was 4 males to one female.

Finger clubbing may begin at any age. The youngest patient in this series was a girl 3 years old, a case of congenital heart disease, and the oldest was a man aged 84 years suffering from a bronchial carcinoma.

Clubbing of the fingers is usually asymptomatic. 96·8 per cent. of patients in this series complained of no subjective symptoms. Symptoms were present in 3·2 per cent. of cases. These comprised a sensation of undue warmth, tingling in the finger tips, sweating of the fingers and hands and an increased growth of the nails.

The earliest sign of finger clubbing is an increased fluctuation of the nail bed. This is rapidly followed by thickening of the fibro-elastic tissue at the base of the nail resulting in a filling out of the angle between the nail and the basal tissues. The nail bed then appears pink and shining while the skin is stretched over this area obliterating the normal creases. Alteration in the curvature of the nails in their sagittal and coronal planes then occur with associated increase in their longitudinal ridging. The nails become more brittle and grow more quickly. The cuticle increases its rate of growth and keeps pace with the nail; the lunule therefore becomes obliterated by this rapidly growing cuticle. Later there is hyperplasia of the soft tissues in the

pulp of the finger tips causing the fingers to have the typical bulbous appearance.

These changes then progress to hypertrophic osteo-arthritis. According to Frangenberg this may develop any time from six months to twenty years after the onset of the clubbing. Hypertrophic osteo-arthritis usually gives rise to no symptoms, but in advanced cases aching pains may be experienced around the wrists and ankles and in the shafts of the long bones which are usually tender. Gluzinski states that this pain and tenderness may be worse in women at the time of menstruation. Penitschka has described effusions into the joints in a case of hypertrophic osteo-arthritis. There may also be muscular weakness in the affected limbs. It may be difficult to determine, however, whether this latter symptom is due to the primary causative disease or to the local changes in the bones and joints.

A very characteristic feature of clubbing of the fingers is the exacerbation and remission of the condition. This waxes and wanes with the activity of the primary disease. Lissard, in fact, states that clubbing may be regarded as the barometer of the underlying pathological process. Clubbing of the fingers has disappeared in several cases in this series following :—the drainage of an empyema ; the operation of lobectomy for bronchiectasis, for lung abscess and for bronchial carcinoma ; the medical treatment of amoebiasis and of sprue and in a certain number of cases the clubbing has disappeared, in subacute bacterial endocarditis after penicillin therapy. Puig has reported the disappearance of even hypertrophic osteo-arthritis, following treatment, in a patient with a pulmonary abscess. Moulonquet and Salamon described clubbing in 2 patients suffering from colitis and stricture of the rectum ; in both cases the clubbing cleared up following colectomy and rectal lavage. Thomas described a decrease in the degree of clubbing in a case of post-thyroidectomy myxoedema after the administration of thyroid extract. Blalock and Taussig have shown that clubbing receded in their patients who were operated upon for the tetralogy of Fallot and Smith quotes a case in which ligation of an aneurysm of the subclavian artery resulted in the disappearance of the clubbed fingers on the affected side.

Several names and similes have been applied to clubbed fingers depending upon the stage of development and degree of this phenomenon. When the nails first become curved the clubbing is known as the watch-glass type. When the nails are curved in the sagittal plane and there is filling out of the angle between the nail and the nail base the clubbing is described as the parrot-beak variety. Drum-stick clubbing is the name given to this phenomenon when soft tissue hyperplasia is very marked. Bauer has likened this latter condition to a clock pendulum and Frangenberg to a serpent's head. The French, however, still refer to finger clubbing as Hippocratic fingers.

Horsfall and Mendlowitz have stressed the difference between acquired and hereditary clubbing of the digits. The clubbing of the

hereditary type may involve different fingers and toes to a varying degree while in the acquired lesion the clubbing is generally uniform. Another feature of hereditary clubbing, described by Seaton, is that it usually begins at the age of puberty and may become very marked in middle age. Both Seaton and Mendlowitz have described a great increase in the degree of hereditary clubbing in patients with the onset of hypertension. Complete disappearance of the clubbing is never seen in the hereditary type.

### X-RAY APPEARANCES

There are usually no radiological changes in the fingers in the early stage of clubbing. Later there may be enlargement of the ungual process and osteoporosis of the terminal phalanges. Weens and Brown have reported 2 cases where atrophy of the terminal phalanges was the presenting radiological sign. Hypertrophic osteo-arthritis is characterised by an irregular periosteal thickening of the shafts of the involved bones. This occurs first in the proximal phalanges and metacarpals and later spreads to the other bones. In advanced cases the subperiosteal new bone formation may be so pronounced that marked thickening of the shafts of the bones result. The bones most frequently affected are the proximal phalanges, the metacarpal and metatarsal bones, the long bones of the extremities and the clavicles. The vertebræ and ribs are rarely involved.

### DIFFERENTIAL DIAGNOSIS

Clubbing of the fingers must be differentiated from acromegaly, a condition with which it was at first confused by Erb and Fraentzel. Osteo-arthritis, rheumatoid arthritis, Heberden's nodes, syphilitic or tuberculous dactylitis and brachydactyly may also be confused with finger clubbing.

### SIGNIFICANCE OF FINGER CLUBBING

(1) Unilateral clubbing should suggest some condition affecting the vessels or nerves of the arm or at the thoracic outlet.

(2) Bilateral clubbing, however, may indicate the presence of many underlying diseases. If present in association with some cardiac disease then the probability of subacute bacterial endocarditis is very likely, although clubbing of the fingers may occur in advanced cases of mitral stenosis with congestive failure and also in chronic active rheumatic endocarditis. Congenital heart disease should also be considered in this connection.

(3) If there are symptoms or signs referable to the respiratory system and clubbing is present then some septic process in the lung, or a bronchial carcinoma is the most likely cause.

(4) When clubbing is associated with gastro-intestinal symptoms, then chronic bacillary or amoebic dysentery, ulcerative colitis, sprue or biliary cirrhosis are probably present.

(5) Clubbing may occur without any other associated symptoms. In this case bronchial carcinoma must always be considered as the following case illustrates:—A man, aged 41 years, complained of swelling of the fingers and sweating of the hands for four weeks. Examination revealed a partial collapse of the right middle lobe of the lung. He was found to have a bronchial carcinoma which up to then had remained silent.

(6) Finger clubbing may be discovered incidentally during the investigation for some other disease. Here again a carcinoma of the bronchus must be kept in mind. This is illustrated by the following 4 cases. A patient, aged 56, developed a paraplegia. Clubbing of the fingers was noted and a mass at the hilum of the right lung was detected on radiological examination. Another patient, aged 54 years, had pain in his right shoulder and bilaterally clubbed fingers. He had a carcinoma of the bronchus producing collapse and infiltration of the right upper lobe of the lung. A man, aged 49 years, suffered from Jacksonian epilepsy, headache and difficulty in speech. Finger clubbing was noted on examination and an X-ray showed an opacity at the hilum of the left lung. Finally, a patient, aged 55, was admitted suffering from a pneumothorax. Marked finger clubbing was noticed and a bronchial carcinoma was detected on further examination.

(7) Digital clubbing can indicate the progress of the causative disease waxing and waning with the activity of the disease process. It may disappear following the drainage of an empyæma or the treatment of subacute bacterial endocarditis with penicillin. If clubbing is still present after apparent appropriate therapy, failure to eradicate the disease must be considered or some other underlying hitherto unsuspected lesion is present, *e.g.* an empyæma and a bronchial carcinoma.

### THE MECHANISM OF FINGER CLUBBING

There are many theories as to the ætiology of clubbing of the fingers.

Laennec suggested the condition was caused by wasting of the soft tissues in the proximal more than in the distal phalanges. Pigeaux, on the other hand, suggested that clubbing was due to œdema of the connective tissues of the distal phalanges. Von Bamberger and Marie stated that clubbing of the fingers was produced by the effects of toxins. Brooks elaborated this theory and postulated that toxæmia caused capillary dilatation with local anoxæmia in the tips of the digits. Other writers support Brooks and suggest that clubbing is due to metabolic toxins produced by the breaking down of body tissues which occur in cases of empyæma or bronchial carcinoma, the toxins causing a vaso motor disturbance with peripheral dilatation of the capillaries. Mendlowitz studied the peripheral blood flow in individuals with clubbing of the fingers and found the blood flow to be augmented and to be accompanied by peripheral vasodilatation. He concluded

that increased peripheral blood flow will form a corner stone of the future theories as to the mechanism of clubbing and hypertrophic osteo-arthropathy. Against this theory, however, is the fact that clubbing is not seen in cases of thyrotoxicosis nor does it appear following sympathectomy.

Cases who show finger clubbing can usually be divided into three main groups :—

- (a) Those in whom anoxæmia is the main feature.
- (b) Those in whom there is some element of toxæmia.
- (c) Where both anoxæmia and toxæmia co-exist.

It is well known that finger clubbing disappears following the treatment of lung abscess or empyæma and Blalock and Taussig have shown that clubbing receded in their patients who underwent successful operative treatment of Fallot's tetralogy. It would thus appear that both anoxæmia and toxæmia are important factors in the causation of finger clubbing.

#### (a) *The Anoxæmic Factor*

Many investigators including Haldane and Priestley, Hooker and Krogh have pointed out the association of vaso-dilatation with anoxic states. The arterial anoxia present in some types of congenital heart disease may thus produce the peripheral vaso-dilatation described by Mendlowitz and also render the tissues anoxic, thereby stimulating the fibrous tissue in these parts to proliferate and thus producing the picture of clubbing of the fingers.

#### (b) *The Toxæmic Factor*

The mechanism of clubbing in such conditions as bronchiectasis, hepatic cirrhosis and ulcerative colitis, however, demands further explanation. All these conditions are associated with a degree of toxæmia and the majority of these cases have an increased blood sedimentation rate. This increased B.S.R. is common to the majority of cases characterised by clubbing of the fingers, although it is recognised, that clubbing does not occur in certain long-standing infections and in other conditions associated with an increased sedimentation rate. The rate of fall of the R.B.C. therefore demands further study.

(1) *The Blood Sedimentation Rate.*—In any sedimenting system there are two components which must be considered, viz. :—the suspending medium and the substance suspended. In the case of blood the plasma is the suspending fluid medium and the R.B.C. the suspended material. Nicols stated that of the many factors which influence the rate of fall of the R.B.C. the most important are :—

- (i) The number and size of the R.B.C.
- (ii) Rouleaux formation and agglutination. The rate of sedimentation varies directly with the speed of rouleaux formation and the size of the subsequent agglutinated R.B.C.



- (iii) Protein fractions—changes in plasma proteins influence the rate of the B.S.R.
- (iv) Cholesterol and lecithin. Changes in these substances are said to be accompanied by an increase in the B.S.R.

(2) *The Blood Sedimentation Rate and Plasma Proteins.*—It has been known for many years that a high B.S.R. is usually due to an increased concentration of fibrinogen or globulin, or both in the plasma. The origin and the significance of the quantitative changes may of course vary. In infections globulin antibodies increase the globulin fraction and the primary infective agent may stimulate the production of fibrinogen. In many diseases accompanied by a high B.S.R. the cause of the protein change is, however, less obvious or even quite obscure. Serum globulin is not a uniform compound. Electrophoresis has demonstrated that serum globulin consists of three well-defined components designated as  $\alpha$ ,  $\beta$  and  $\gamma$  globulin respectively. Each component may vary in disease. Luetscher has demonstrated a fall in the serum albumen and a rise in the  $\gamma$  globulin and perhaps the  $\beta$  fraction in cases of cirrhosis of the liver. Similar cases have been described by Waldenstrom and Malmos and Blix. The latter authors found a reduction in the albumen, an increase in the  $\gamma$  globulin and fibrinogen in the plasma in cases of rheumatic fever. They also demonstrated that the globulin and fibrinogen were increased without exception in cases of chronic infections. Malmos and Blix have also shown that the correlation between the B.S.R. and the different globulin fractions will vary according to the clinical material used. In chronic infections there is a definite correlation between the  $\alpha$  and  $\gamma$  globulins and the B.S.R. The acceleration of fall of the R.B.C. is related therefore to the levels of the fibrinogen and globulin. The B.S.R. varies directly with the concentration of these proteins and altered concentration causes the R.B.C. to stick together and results in the formation of rouleaux.

(3) *The Blood Sedimentation Rate and Blood Flow.*—Fahraeus studied the capillaries of the nail bed and noted a uniform flow of blood in normal individuals, while in those with an increased sedimentation rate varying degrees of granularity were present and the flow of blood was broken by stretches of clear plasma.

(4) *The Blood Sedimentation Rate and Rouleaux Formation.*—In health, due to the biconcave configuration of the erythrocyte, the maximum cell surface area is thus made available for respiratory exchange. It is apparent that the function of the R.B.C. which have lost this ideal configuration by reason of rouleaux formation will be impaired. Fahraeus noted that not only were the aggregates of R.B.C. larger in the rapidly settling blood but had also a more solid structure. There are therefore two factors which influence the respiratory surface in this abnormal state of the blood, the size of the rouleaux and their fragility. Gaseous exchange will therefore be interfered with, depending on the number of cells in each clump, and therefore in proportion

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to the level of globulin and fibrinogen and the rate of the blood sedimentation.

(5) *Blood Flow and Rouleaux*.—It is apparent that the rouleaux must traverse the circulation, and, it is clear that if they are large enough and sufficiently stable they may adhere to the walls of the capillaries and perhaps later, if the rouleaux formation is broken up, form the sludged blood phenomenon of Kinsley *et al.* On the other hand it may be, that due to the increased rate of blood flow described by Mendlowitz in these cases of clubbed fingers, the rouleaux pass through the tips of the extremities with such rapidity that they do not have time to release their oxygen content. Mauer has suggested that the rouleaux may escape through the arterio-venous anastomosis which are so numerous in the fingers and toes. This suggestion, together with the rapid blood flow may cause low oxygen tension in the digital tissues even though there is a high level of arterial oxygen saturation.

Tissue anoxia may thus exist in infections and neoplasms though the arterial saturation is normal. Rapid rates of blood flow and low tissue oxygen tension provide the same mechanism for clubbing in these states as in the classical cases of arterial anoxia.

#### (c) *Anoxæmia and Toxæmia*

The most severe and the most rapidly developing clubbing are seen in bronchial carcinoma and in empyæma and lung abscess. In these cases the B.S.R. is rapid and arterial anoxia is also present. Hence in certain cases the two types of anoxia may co-exist.

### DISCUSSION

Tissue anoxæmia due to a definite arterial anoxia or a relative anoxia caused by vaso-dilatation, rapid blood flow and increased rouleaux formation, or a combination of both factors is a possible explanation of finger clubbing.

This mechanism can explain the finger clubbing of empyæma, lung abscess, certain cases of bronchiectasis, bronchial carcinoma and silicosis complicated by septic infection. Finger clubbing is met with, however, in certain uncomplicated cases of silicosis. Heimann has observed an increase in the rate of the red cell sedimentation in simple cases of silicosis, the finger clubbing in these cases can therefore be explained by arterial anoxia and also by the increased rouleaux formation. In pulmonary endarteritis and congestive heart failure arterial anoxia is suggested as the possible cause of the clubbed fingers seen in these conditions. In subacute bacterial endocarditis and in chronic active rheumatic heart disease there is a combination of cardiac failure, with its resulting anoxæmia, and infection, with a change in the plasma proteins. Another factor to be considered in these cases is the alteration in serum cholesterol which Poindexter and Bruger have found in rheumatic heart disease with cardiac failure. This factor will also influence the speeds of sedimentation and rouleaux

formation of the red cells. The finger clubbing seen in congenital heart disease is primarily due to arterial anoxæmia.

In œsophageal carcinoma and pyloric stenosis there is a change in the plasma proteins due to the starvation, apart from any alteration produced by the primary disease. Here again increased rouleaux formation indicated by a fast B.S.R. may well be the mechanism of the clubbing in these conditions. In all the cases of chronic diarrhœa in which clubbing is encountered the alteration in plasma proteins resulting from malabsorption or from the chronic infective state may well be the underlying mechanism of the digital clubbing. In addition, any change in cholesterol due to malabsorption must also be considered. The change in the serum globulins seen in parenchymatous liver disease, together with any alteration produced by the chronic infection offers an almost too easy explanation for the clubbing in biliary cirrhosis and amœbic hepatitis.

In the miscellaneous group of finger clubbing definite anoxæmia or relative anoxæmia, which, it is suggested, occurs in toxæmia, or a combination of both mechanisms, can explain the clubbing in these cases and, indeed, offers a link between many apparently unassociated conditions.

Unilateral clubbing may be explained by local anoxæmia in the affected limbs caused by pressure in the thoracic outlet. The explanation of unidigital clubbing is not known.

Although the above theory offers a possible explanation for most of the causes of clubbing of the fingers it does not satisfy all cases. It does not explain hereditary or unidigital clubbing. Instances of tuberculosis and bronchiectasis of many years duration have been observed in which clubbing is not present. Mauer suggests that these are the individuals with little or no systemic reaction, perhaps a low fibrinogen and globulin and normal sedimentation rates. Conversely in rheumatoid arthritis clubbing is rare although the B.S.R. is very rapid. In this condition, however, the blood flow is poor and the tissue temperature is low. This has been offered to explain the absence of clubbing in rheumatoid arthritis. In the nephrotic syndrome and in myelomatosis the B.S.R. is extremely rapid and hyperglobulinæmia is present yet clubbing is rarely encountered.

No adequate explanation of the mechanism of clubbing of the fingers has as yet been found. Possibly there are many factors concerned and more than one explanation.

#### SUMMARY

Diseases in which clubbing of the fingers are encountered are enumerated. The pathology, clinical features, differential diagnosis and significance of finger clubbing are described and some theories as to the mechanism of this phenomenon are discussed.

I wish to thank Professor D. M. Lyon for allowing me full access to the case material.

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# A CASE OF LONG-STANDING TUBERCULOUS INFECTION WITH RECURRING ATTACKS OF ERYTHEMA NODOSUM AND ERYTHEMA MULTIFORME

By Professor CHARLES CAMERON

MISS E. G., 35 years, was admitted to the Sanatorium on 4th August 1948 after biopsy of an axillary gland had shown the presence of caseating tuberculosis. There was no family history of tuberculosis but during two years after 1945 she was in intermittent, although not close, contact with a friend who had lung tuberculosis. That fact probably is of little significance in the history.

## HISTORY OF ILLNESS

In 1936, when she was aged 24, she had a right pleural effusion. The illness was a febrile one and was associated with sweating and bodily weakness. She was treated at home and in bed for three months and a month later resumed work. During the following three years she was kept under observation at the Royal Victoria Dispensary and remained well apart from the following development.

Two years after the pleurisy in 1938, at the age of 26, she noticed that her legs, which had hitherto been slim, were becoming thicker. The swelling was painless and involved the lower third of each leg. The skin in these areas became livid and, in her own words, looked as if it were "frozen with the cold." The underlying tissues were thickened. The swelling and lividity varied from time to time and improved with rest in bed and during warm weather.

In 1942—she was then 30—she detected accidentally some hard lumps in her right axilla. The swellings were painless and have varied little in the intervening years. She was then working as a land girl in the Animal Diseases Research College, Gilmerton, and from time to time handled mice which had been experimentally infected with tuberculosis. The work was intermittent. It was the duty of another girl and E.G. acted merely as a relief when she was on holiday. The periods of duty never exceeded fourteen days and altogether she had about six or eight such spells of this work. It was during one of these spells that she pricked a finger of her right hand. The accident occurred while she was pruning a rose bush and did not occur in the animal house. Twenty-four hours later glands in the left axilla became swollen and painful. They subsided in a day or two and a few weeks later she detected the painless glands in the right axilla. There was probably no causal connection between the two conditions.

Demonstrated to the Tuberculosis Society of Scotland at a meeting held in Southfield Sanatorium on 22nd October 1948.



In 1945, when she was aged 33, she began to have attacks of what she calls "fullness of the head" and dizziness. The attacks lasted for a few days and the tendency to the condition lasted for two years. She was very tired at this time and her doctor noticed enlargement of the thyroid gland. He sent her to one of the physicians in Edinburgh Royal Infirmary and she was taken into his ward for investigation. She was found to have a red blood cell count of over six million and, according to her statement, she was advised to become a blood donor. For a period of one and a half years she gave a pint of blood every three months.

In 1947, a little more than a year ago, she began to develop crops of spots on the legs below the knees. In all she has had six or seven attacks. Both legs have been affected simultaneously and the spots have appeared both on the front and back of the legs, but principally on the back. She describes them as large, red, itchy, and raised, and says that she could pick them up like hard masses in the skin. They varied in size up to that of a half-crown piece, lasted for about two weeks, and gradually disappeared. The lumps sometimes formed small yellow centres and looked as if they were going to break down, but they never ulcerated. During the attacks she felt very exhausted and still felt tired even after sound sleep. She sweated a great deal. The lower thirds of the legs were much more swollen during the attacks and she described the swelling at these times as "hanging over the ankles." The bones in the areas of swelling felt tender, and cough, never present at other times, was a troublesome symptom.

In June 1948 she had the worst attack which she has experienced. A week after the appearance of the nodules she suddenly developed stiffness of both knee joints, of the right elbow, and of the left wrist. Twenty-four hours later the joints became swollen and painful, but the skin was not reddened and there was no superficial heat. She felt tired, but there was no fever and no sweating. The pain lasted for two weeks and the joint stiffness lasted for a further similar period. The joint attacks led to her admission to Professor Davidson's rheumatic clinic and there a gland was excised from the right axilla. The gland was found to be tuberculous and I was asked to see her. On account of the interest of her case I admitted her to the Sanatorium.

#### CONDITION ON ADMISSION

She was then well nourished, of good colour, and in very good general condition. She weighed 10 stones and her height was 5 feet 6 inches. The salient points in the physical examination were slight flattening of the right side of the chest, and the presence in the medial wall of the right axilla of three small hard glands approximately of the size of cherry stones. A larger gland had been excised. There was a peculiar soft tissue thickening of the skin and underlying tissues of the lower third of each leg, and on the front

of the right leg in this site there was a wide oval area of violaceous skin discolouration. There were palpable irregularities of the margins of the right tibia. There were no scars. All of her joints appeared to be normal. The X-ray film of the lungs showed flattening of the right diaphragm and partial obliteration of the right costo-phrenic angle. A film of the lower leg bones showed no abnormality.

She was tested by the Mantoux method with 0.1 ml. of 1 : 10,000 old tuberculin. The reaction was violent. At the end of twenty-four hours the central œdema had a diameter of 30 mm. At seventy-two hours this area had become hæmorrhagic and the surrounding erythema covered an area of 100×110 mm. The B.S.R. (Westergren) on admission was 29 mm. Seventeen days later it was 45.

Fourteen days after admission she developed an attack of erythema multiforme of the purpuric type involving principally the hands, the outer aspect of each elbow, and the back of the right leg below the knee. This was associated with an erythematous face rash. The eyes and mouth were not affected. Dr Grant Peterkin kindly saw her in the Royal Infirmary and supplied the diagnosis. Within twenty-four hours of the appearance of the rash the site of the tuberculin reaction, which was fading, became intensely red and painful. There was no alteration in the state of the glands and the attack subsided in ten days. There was no eosinophilia.

This attack led to more precise interrogation and she then told me that she had had many similar attacks during the past ten years; the first started two years after the pleurisy. The attacks were always in the summer and were definitely related to sun exposure. Her mother suffers from bronchial asthma.

Complete blood investigation was only made on 10th October, more than two months after her admission and six weeks after the disappearance of the erythema multiforme. It yielded the following results:—

Red blood cells 4,640,000.

Hæmoglobin 94 per cent.

Colour index 1.

White cells 7000 per c.mm.

A differential count showed neutrophils 52 per cent., basophils 2 per cent., large lymphocytes 14 per cent., small lymphocytes 19 per cent. and monocytes 13 per cent. The serum protein was normal—albumen 4.6 per cent. and globulin 2.5 per cent.—total 7.1 per cent. The count was repeated on 16th October with a similar finding, the monocyte percentage being 12.

## DISCUSSION

Her case presents several points of interest. The swelling of the lower areas of the legs which appeared suddenly two years after the pleurisy was, from her description, of the acro-cyanotic type which

frequently precedes and accompanies some of the tuberculides, and the interest lies in the sudden appearance of the circulatory change. The diagnosis of the nodular eruption which appeared nine years later lies between erythema nodosum and erythema induratum, and the tendency of the nodules to involve the backs of the legs suggests the latter condition. None of the nodules, however, ulcerated and the comparatively short duration of the attacks with the accompanying general symptoms is more suggestive of erythema nodosum. Her description of the lesions too favours that condition and the association of the last and most severe attack with polyarthritis makes it almost certain that the condition was in fact erythema nodosum. The recurrence of these attacks is then of interest.

A good deal of the recent literature on so-called nodal fever has come from the Scandinavian countries. Ustvedt (1947) has recently pointed out that the views held in Norway on the ætiology of the condition are very much the same as those held here. In a recent series of 200 cases he found in 26 per cent. overwhelming evidence of a non-tuberculous ætiology and in 66 per cent. he found convincing evidence of a tuberculous basis. One gets the impression from the Scandinavian literature that the condition occurs at a certain phase of the primary infection when allergy has become established, and Frostad (1946) in his interesting publication on early lung lesions in their relation to the primary infection used an attack of erythema nodosum, when it occurred, as marking a primary infection which had become established a few weeks earlier. Kayne, Pagel and O'Shaughnessy (1939) state that it occurs early in the stage of dissemination when the allergic hypersensitivity is high and they group it with phlyctenular conjunctivitis. The general implication is that erythema nodosum is a condition which occurs once and then at a definite stage of the infective process. Yet we know that many attacks of phlyctenular conjunctivitis may take place, and this recurring nature of the condition in tuberculous children of a certain strumous type is one of its most troublesome features. It is generally believed that both conditions are allergic phenomena and cutaneous sensitivity to tuberculin is almost invariably high. Although recurring attacks of erythema nodosum are rare they do occur, and the first manifestation may appear long after the primary infection. In E.G.'s case it came eleven years after the pleurisy with effusion, nine years after the development of the acro-cyanosis which is of course a non-specific condition, and five years after she first detected the presence of enlarged axillary glands. The view that erythema nodosum occurs at the end of the incubation period when the pre-allergic phase passes into an allergic phase is endorsed by Forssman (1946) who remarks that the rash has in fact been termed the autogenous tuberculin reaction of the body; but he adds that it may in some cases occur in the later stages of tuberculosis and that a patient may have several relapses. He quotes Wallgren for the statement that this is apparently due to

allergic variations caused by intercurrent diseases. Ustvedt (1942) states that recurrent attacks of erythema nodosum are not uncommon in adults (10-20 per cent.) and that later attacks have been explained as being due to fluctuations in allergy. There is no history of a tuberculin test having been carried out on this patient before her admission to Edinburgh Royal Infirmary and consequently we know nothing about her previous skin sensitivity to tuberculin.

Rich's work has done much to clarify our conception of the relationship of allergy to immunity. In clinical work it is extremely difficult to dissociate the two conditions and we have no proof that the sensitivity of the skin represents accurately the degree of allergy of any of the other tissues. Theoretically a high degree of sensitivity is dangerous, and many of the destructive phenomena of tuberculosis are due to the allergic state of the tissues; but patients can have a high degree of clinical immunity with all degrees of allergy as represented by the skin response to tuberculin. There are certain types of tuberculosis in which skin sensitivity is high, particularly glandular types especially when a scrofulodermatous infection has taken place; and children of the flabby exudative type who are prone to eczema often suffer from a sluggish type of lymphatic tuberculosis characterised by extreme degrees of skin sensitivity to tuberculin. This in fact is the type of tuberculous child which is prone to phlyctenular conjunctivitis, and is a type which usually ultimately does extremely well under good conditions of diet and hygiene. The majority of nurses who have worked for a long time in pulmonary tuberculosis wards are extremely sensitive to the skin tuberculin test and it is interesting to contrast their extreme cutaneous sensitivity with their good general condition. We believe that in their case, allergy is constantly stimulated by repeated infection. If that is so, their immunity must be kept at a correspondingly high level. I have never seen an attack of erythema nodosum in these nurses, nor in the post-initial period of the illness of those children which I have discussed. In connection with the possibility of superinfection in E.G.'s case I do not believe that the history which she gave of exposure to infection from a tuberculous friend after 1945 had any effect on her sensitivity or immunity. The friend was an early mass radiography case and was apparently leading a normal symptomless life at home. The reactivation of the Mantoux reaction during an attack of erythema multiforme demands a discussion of that condition.

The ætiology of erythema multiforme is unknown and I do not propose to attempt to discuss a condition with which I am unfamiliar. It has been classed as allergic and occurs not infrequently in association with focal sepsis. E.G.'s throat was healthy, and a complete examination of her mouth by a dental surgeon and a complete radiographical examination of her teeth revealed no evidence of disease. We found no other focus of infection. She has had these attacks for ten years and whether they have any relation to her high

tuberculin sensitivity is a point for discussion. According to Ustvedt (1942) erythema multiforme is sometimes seen in association with erythema nodosum in proved cases of primary tuberculous infection and may occasionally occur alone in these cases. He grants, however, that it is much more frequently due to other causes than is erythema nodosum. Of more direct interest is the reactivation of the Mantoux reaction to which I have referred.

The delayed tuberculin reaction is a well-known phenomenon. Sixty cases were observed during the course of the Prophit Trust Survey (1948) and the condition was discussed by Daniels (1943) in an earlier communication. In these cases there was no reaction at the time of testing, but several weeks after the test, in 15 of the cases the interval was from three to eleven months, a reaction appeared at the site of the last injection which was made with 0.1 ml. of 1 : 100 old tuberculin. In a high percentage of these cases re-testing after the appearance of the delayed reaction showed a high degree of cutaneous sensitivity. As quoted in the report a similar phenomenon has been observed in brucellin testing. The reactivation of a previously positive test site is probably a similar phenomenon. In each case it is believed that tuberculin is held in the tissues. The delayed reaction is due to the appearance of allergy at a later date either from a developing, or from a later, infection. The reactivation phenomenon is less easily explained and in this case we cannot exclude the possibility of it being a Shwartzman reaction. It has been proved (Rich, 1944) that inflammatory local tuberculin reactions in hypersensitive animals may become hæmorrhagic when various bacterial filtrates are injected into the blood stream, and that may be the explanation here if we do not accept the erythema multiforme as being of tuberculous origin. Rich also discusses the accumulation of injected tuberculin in areas of tuberculous disease and states that many types of foreign substance when introduced into the blood stream escape at inflamed sites and are retained there, reaching concentrations which are much higher than those which exist in normal areas of the same organ. If we assume that the erythema multiforme was an allergic response to an increased absorption of tuberculo-protein from a tuberculous focus its concentration at the site of the old destructive tuberculin reaction, and the reactivation of the reaction, are readily understood.

A case recently recorded by Bordet (1946) adds considerable interest to these speculations. This was a girl of 19 who had had in the course of her life three tuberculin tests performed. The mode of testing is not stated. The first test was carried out four years previously and was negative. The second was done sixteen months previously and gave a doubtful reaction. The third was performed four months previously and was strongly positive. In June 1944, four months after this last test, she developed suddenly in the left deltoid region in the sites of the tuberculin tests three big hard livid nodules situated one above the other. She had had contact with an

infectious consumptive and had been ailing since the previous January. Two other similar nodules appeared, one in the right upper eyelid and one on the right cheek. A biopsy of one of the arm nodules showed tuberculous follicles with necrotic centres, and guinea-pig inoculation was positive. Four months later she developed "rheumatic manifestations of the Poncet type" and ten months after the appearance of the nodules died of tuberculous meningitis. During her illness a few other isolated tuberculous gummata appeared in various scattered sites of the skin and their dispersal and distribution left no doubt in Bordet's mind of the fixation rôle which the old skin tuberculin tests played in localising circulating tubercle bacilli. He states that tissues previously impregnated with tuberculin, whether they have reacted positively or not, acquire and retain not only a special sensitivity to circulating tuberculosis toxins but also to the bacilli themselves which they may actually localise.

Here then is a case of long-continued tuberculous infection characterised, in the later stages at least—we have no knowledge of her previous state—by a very high degree of cutaneous allergy and by a very high degree of immunity. An initial attack of pleurisy was followed a few months later by acrocyanosis of the lower legs and six years later by enlargement of glands in the right axilla which were later proved to be tuberculous. The significance of the polycythæmia which appeared three years after the glands were noticed is doubtful. It was apparently an evanescent phenomenon. I lay no stress on the polyarthritis as a separate phenomenon. It accompanied a severe attack of erythema nodosum which was presumably of tuberculous origin, and I have avoided complicating the issue by discussing separately the question of tuberculous rheumatism which is probably an allergic phenomenon identical with the polyarthritis which is such a frequent accompaniment of erythema nodosum. A history of polyarthritis in the early stages of their illness is often given by tuberculous patients and there is little doubt that it occurs frequently in the early allergic period with, or without, accompanying erythema nodosum. I am referring here to the arthralgic or evanescent acute types of the condition and not to the very uncommon chronic polyarthritic and rheumatoid types. The condition has recently been discussed by Sheldon (1946). The attacks of erythema nodosum appeared at a late stage of her illness and recurred several times in a space of eighteen months. That is a sufficiently unusual phenomenon to warrant discussion as also is the relationship of the erythema multiforme which appeared two years after the initial pleurisy and has recurred at yearly intervals. The association of a high degree of cutaneous allergy with obviously high immunity is a familiar, but in the light of some writings, interesting clinical fact. Two more points are of minor interest. Despite a good general condition the B.S.R. remains high and the blood monocyte

count is above normal. Is that of significance, and can minor blood cell variations be related with any accuracy to specific pathological tuberculous processes? The work of Medlar, Sabin, and others in this field cannot be lightly disregarded. It is generally held that an increase of the circulating monocytes and an alteration of the monocyte-lymphocyte ratio indicates a proliferation of tubercle bacilli in the tissues and the formation of fresh tissue lesions. If that is so the balance struck in this patient's case between the highly allergic and the immune states must be precarious and we are probably justified in paying serious attention to the probable significance of these two findings.

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# SUBACUTE BACTERIAL ENDOCARDITIS AND ITS TREATMENT WITH PENICILLIN

By

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THE introduction of a new and effective remedy for a serious and usually fatal disease rapidly creates fresh problems. Consideration of the response to treatment, in particular the changed course of the illness, and the alterations in the pattern of the disease thus induced, commonly reveals serious gaps in our knowledge of the essential mechanisms of the disease and of their influence on the usual sequence of events. In addition to saving life, a reliable remedy therefore contributes to our knowledge of the fundamentals of the pathological process. This has been true of diabetes, pernicious anæmia and thyrotoxicosis. We believe that bacterial endocarditis is no exception to the rule.

For many years emphasis has been placed on pre-existing endocardial damage with a superimposed septicæmia of recent origin as the essential factors in the production of this serious malady. The nature of the focal infection, the portal of entry, the persistence of the blood-stream infection even for months or years, the character of the ulcerative lesions engrafted on the rheumatic valves and the consequences of multiple emboli in the kidneys, brain and elsewhere, have long provided a wealth of pathological material and a sequence of events impressive in their relentless capacity to destroy. To the student the disease process was clearly demonstrated but until recently the clinicians faced with the problems of treatment were as powerless as the pathologists were omnipotent. The death rate was 99 per cent. (Lichtman, 1943).

## ETIOLOGICAL CONSIDERATIONS

In recent years emphasis has been placed on a number of etiological factors of increasing importance both in prevention and treatment of this disorder. Oral sepsis is a well-worn theme but in bacterial endocarditis the evidence for incrimination of the teeth is overwhelming. The *streptococcus viridans*—the commonest organism recovered from the blood of patients suffering from bacterial endocarditis, is an indigenous parasite of mucous membranes, a normal inhabitant of the

An Address to the Medico-Chirurgical Society of Edinburgh, on the 19th January 1949.



mouth, and low in virulence. It grows luxuriantly in fibrin uninhibited by the presence of specific antibodies (Rosebury, 1944).

From a study of 40 cases of subacute bacterial endocarditis in which gross dental sepsis was present in 17 and amongst which 4 had had dental extractions shortly before the onset of the disease, Rushton (1930) put forward the suggestion that oral sepsis was the source of the blood infection, an observation confirmed by Abrahamson (1931) the following year. Okell and Elliott (1935) recovered the streptococcus from the blood five minutes after multiple dental extractions in 75 per cent. of otherwise healthy people and later it was shown by Elliott (1939) that the rocking movements imparted to the tooth before its actual removal, or even ten minutes' mastication in patients with pyorrhœa, were sufficient to induce a transient bacteræmia. How often the alimentary tract may provide the portal of entry it is impossible to estimate, but infection through a breach of the mucous membrane of the rectum, urinary tract or genital passages is not so uncommon. The manual massage of various infected sites such as joints, tonsils, boils and the prostate, has been followed by the recovery of bacteria from the blood even an hour after the manipulation (Richards, 1932). Such an event in health may be of no great importance, the organisms being eliminated from the blood in a short time by normal clearing mechanisms. In the presence of valvular disease, the broken, ragged endocardial surface favours the local implantation of the organism, with the subsequent formation of friable vegetations in which it proliferates freely.

In the prevention of subacute bacterial endocarditis it is necessary to forestall the development of a viridans bacteræmia, particularly when operative procedures on mucous membranes are contemplated, by the preceding administration of sulphonamides begun eight to twelve hours before operation and continued for at least forty-eight hours thereafter. By such means Budnitz (1942) and Nothrop (1944) found that bacteræmia could be prevented after dental extractions. The co-operation of oral and dental surgeons in this way will reduce the incidence of subacute bacterial endocarditis. Incidentally, our experience is that when dental extractions are "covered" with sulphonamides, in such dosage as considered suitable for lobar pneumonia, or with one or two injections of penicillin, each 100,000 units, the amount of oral sepsis is minimal, the gums heal with surprising rapidity, and extensive multiple extractions can be undertaken at a single sitting in cardiac patients with little or no general reaction and with no fear of the development some days later of this serious disease. Doubtless, the same findings apply to operative interference on mucous membranes other than those of the mouth and throat.

Further etiological factors concerning the localisation of the vegetative process are the importance of fully oxygenated blood flowing vigorously over the damaged endothelial surfaces. On the valve leaflets, a short way from the extreme edge and at the sites of contact,

the pathological process begins by the deposition of thrombi and organisms from the blood-stream. Where turbulence is maximum fibrin is "whipped" from the blood and is deposited in polypoid masses on the damaged surface. The importance of these factors is seen in such congenital lesions as the patent ductus, as a result of which, in the presence of a blood-stream infection, the vegetations form in the pulmonary artery opposite the ductal orifice (Fig. 1). At this site turbulence is maximum and a stream of fully oxygenated arterial blood, favouring the growth of the streptococcus, enters the pulmonary

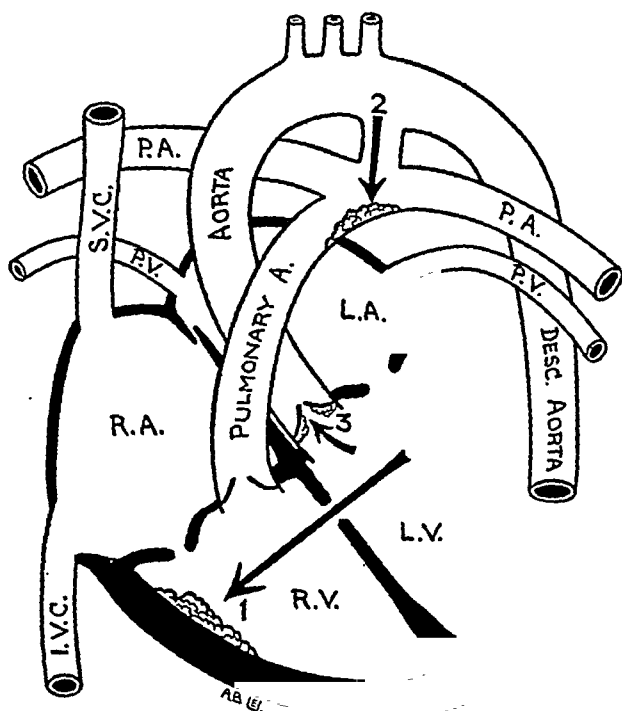


FIG. 1.—Diagram to show the sites at which the bacterial infection commonly becomes localised in certain forms of congenital heart disease. The clumps of vegetations occur in the first instance where turbulence is maximum and usually in the presence of a jet of arterial blood. 1. Patent interventricular septum. 2. Patent ductus arteriosus. 3. Bicuspid aortic valve.

artery. Cross-currents, irregular flow and intra-vascular tension are diminished or eliminated and the  $O_2$  content of the pulmonary artery reduced to that of normal venous blood by the surgical occlusion of the ductus. The septicæmia can be eradicated in a matter of minutes (Touroff, 1942; Gilchrist and Mercer, 1947). Thereafter the vegetative process undergoes resolution without the use of antibiotics—a very remarkable achievement directly attributable to surgical therapy and one unassociated, so far as we are aware, with any tendency to relapse.

Considering the ceaseless activity of the valve leaflets the alterations in the speed and direction of blood flow, particularly over

infected aortic cusps, and the variations in pressure, the buffetings to which the vegetations are thus exposed must be very great. The wonder is that they ever heal and that embolic phenomena are not more common.

The frequency of the disease is difficult to estimate. In the ten-year period 1934-43, immediately before the use of penicillin, 65 proven cases were encountered in the pathological department of the Edinburgh Royal Infirmary amongst a total of 5952 post mortems conducted over the same time. Perhaps 10-12 cases a year in the medical wards of this hospital might be taken as an average intake. Horder (1909-10) calculated that the incidence was 1 in 173 medical admissions to St Bartholomew's Hospital. The sporadic occurrence of a relatively small number of cases scattered throughout the various charges of a large hospital obviously mitigates against the rapid accumulation of knowledge of the most effective measures of treatment. The segregation of these patients in one department of the hospital as urged by the Penicillin Committee of the Medical Research Council was therefore of enormous advantage and we are most indebted to our colleagues on the staff of this hospital and others for so generously placing their patients under our care. Without clinical co-operation knowledge of this disease and its therapeutic control could not have advanced so rapidly. By the selection of various centres throughout the British Isles co-ordinated research according to a pre-arranged plan has yielded results far beyond expectations—results which could not have been obtained in ten years of plodding individual endeavour. Within two years of the start of the enquiry in 1944 Christie (1946) was able to present an analysis of the results of treatment obtained in 269 patients carefully investigated at 14 selected centres. The experience gained at the Edinburgh centre forms the basis of this report.

Although rheumatic heart disease is common, subacute bacterial endocarditis is much less frequently encountered as a clinical entity, the apparent disproportion in frequency being exaggerated by the liability for rheumatic infection to recur again and again in the one individual, whereas until recently subacute bacterial endocarditis has been a uniformly fatal disease. It is said to occur in about 5 per cent. of cases of rheumatic heart disease. Rheumatic valvular disease is the pre-disposing factor in 80-90 per cent. of cases, and congenital heart disease in 5 per cent. or more (White, 1945; Gelfman and Levine, 1942). The incidence of subacute bacterial endocarditis is ten times as high in adults as in children (Gelfman, 1943). Von Glahn and Pappenheimer (1935) believe that the disease develops on unhealed *active* rheumatic lesions, although these may have existed in a sub-clinical form for many years. Support for this view is expressed by MacIlwaine (1945, 1947), who from a pathological study of 34 cases of subacute bacterial endocarditis concluded that at the moment of implantation of the strept. viridans on unhealed rheumatic verrucæ, the heart itself was the site of acute rheumatic lesions, Aschoff nodules

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at various stages of development being detected in 85 per cent. of the hearts examined. The conception of an active rheumatic myocarditis coinciding in time with the development of a bacterial endocarditis is one on which from our clinical studies we place considerable emphasis.

### THE CLINICAL PICTURE

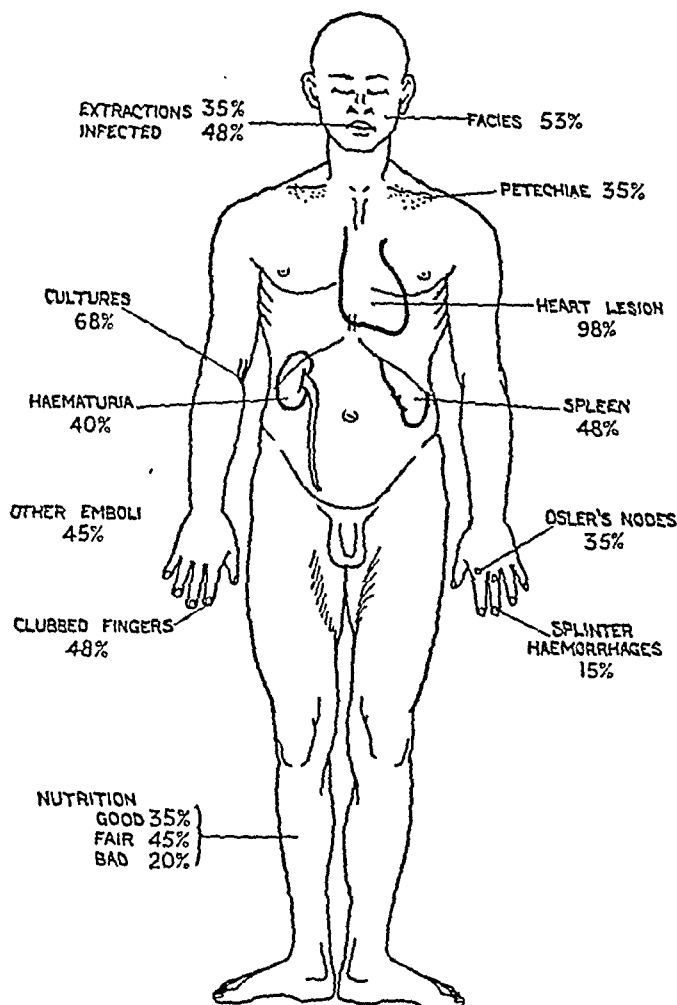
In the pre-penicillin era there was no immediate urgency in establishing a diagnosis: in fact, the tendency was in the opposite direction, as a positive diagnosis virtually amounted to a death sentence, the incidence of spontaneous recovery amongst 2596 cases collected by Lichtman (1943) being 1 per cent. With the employment of sulphonamides the incidence of recovery in 489 cases was only 4 per cent. (Lichtman, 1943). Penicillin yields a recovery rate of 50-60 per cent. so that it is no longer justifiable to allow the disease to unfold itself and await the development of the fully established clinical picture. With an effective remedy at hand, early diagnosis must be urged. The diagnostic triad of endocardial disease, septicæmia and embolic phenomena still holds good.

There is little to be gained nowadays in endeavouring to separate the fulminating, the acute or malignant, the subacute or the chronic forms of the disease, as penicillin in the presence of a sensitive organism is capable of controlling the outward manifestations of the infection in a day or two. The usual subacute variety, running a course of three to eight months in 75 per cent. of patients (Blumer, 1923), has generally an insidious onset in contrast to the more acute forms, but the former classifications made on a time basis are now of little clinical value.

In their description of the clinical features various authors (Blumer, 1923) have drawn attention to characteristic groups according to the leading symptom, for example *the febrile* in which persisting fever with sweatings and chills predominate, *the arthritic* to which we give particular emphasis in relation to prognosis, and *the embolic*, commonly ushered in by a major catastrophe. In a disease so protean in its manifestations and so deceptive in its earliest signs, the primary symptoms experienced by the patient are of great importance.

The onset is usually very insidious and difficult to place in time, but the commonest complaint is loss of strength, lack of vigour, tiredness, weakness or debility. This is commonly accompanied or followed by vague pains in the limbs or joints, loss of weight, chills and a slowly developing anæmia. Such symptoms developing a week or two after a dental extraction are practically diagnostic in the presence of rheumatic or acyanotic congenital heart disease. A debilitated cardiac patient in whom any suspicion of pyrexia exists should be put to bed for regular temperature records. A fever, even of low grade, unexplained after a week's observation in a cardiac patient, particularly a young adult, should immediately suggest the possibility of this diagnosis. The neglect of such a simple rule is emphasised by the

fact that in our series of patients the average duration of symptoms was thirteen weeks before they were admitted to hospital. On the other hand, well authenticated cases have been described in which fever has been absent for months at a time (Coombs, 1922-23 ; Starling, 1922-23 ; Bramwell, 1948).



Average temperature on admission	.	.	.	100.8° F.
" Hb.	"	"	.	70.6 per cent. (Sahli).
" B.S.R.	"	"	.	51 mm./1 hr.
" White cells	"	"	.	12,000 per cu.mm.

FIG. 2.—Diagram to show the frequency and distribution of the commoner embolic phenomena and other signs observed within the first few days of admission to hospital, in our series of 40 consecutive cases of subacute bacterial endocarditis.

Every endeavour should be made to establish the diagnosis before the occurrence of the irremedial damage of major emboli. This implies a familiarity with the details of the disease which may be readily overlooked but which are of the greatest significance in the presence of a valvular flaw and a low grade fever. Intermittent albuminuria

in the absence of congestive failure (with or without the detection of red cells), palpation of the tip of the spleen, the recognition of a tiny splinter hæmorrhage in the nail bed, a "Roth's spot" in the retina, tender toe or finger tips, an Osler's node about the hands or feet, pink (that is, recent and rapidly developing) clubbing of the fingers and toes, are each capable of providing a confirmatory sign with which to establish the diagnosis. Embolic incidents are not peculiar to subacute bacterial endocarditis, but in contrast to those of pure rheumatic heart disease, they are usually minute in the first instance, repetitive, ephemeral, occurring in showers, and are frequent in the skin. Other signs are the advancing anæmia with the café-au-lait

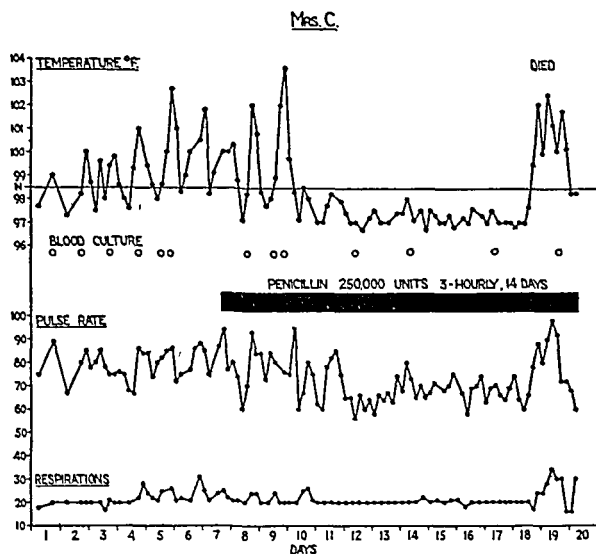


FIG. 3.—The temperature chart of a patient aged 45 from whom blood cultures, made repeatedly, even during rigors, were consistently sterile. She died of a cerebral embolism. Subacute bacterial endocarditis confirmed at autopsy.

complexion which imparts a characteristic facies in the more chronic forms of the disease. Petechiæ in themselves, while suggestive, are less convincing than the other signs (see Fig. 2).

Difficulties arise in various circumstances. The failure to obtain positive blood cultures should not upset the diagnosis. The bacteriological laboratory is not infallible. With the most careful technique (even in febrile patients with rigors), we have obtained consistently *sterile* blood cultures in 32 per cent. of our patients (see Fig. 3). Similarly, an isolated positive culture does not establish the diagnosis and is of much less value than any embolic sign, however small (see Fig. 7). A *succession* of positive cultures, even two or three in the course of the day, taken while the temperature is rising and yielding the same organism, is of course most helpful. Conclusive evidence



of a sustained septicæmia is thus obtained, and the sensitivity of the organism to penicillin may then be determined.

A further stumbling-block in diagnosis is the failure to detect embolic phenomena. For this there is only one remedy, a meticulous examination of the patient from day to day, with special attention to the fingers, retinæ and urine. It is seldom that evidence of organic valvular disease is lacking. Horder (1909-10) found no evidence of a valve flaw in 3 of his 150 patients. Occasionally, conclusive auscultatory signs only appear late in the disease as a result presumably of a spread of the vegetations from the thickened rheumatic endocardium of the left auricle (McCallum patch) to the mitral leaflets. It is worth noting that it is not the advanced mitral stenosis or the free leak of aortic incompetence which is most prone to bacterial endocarditis. The slighter degree of valvular damage most frequently acquires the infection.

The differentiation of subacute bacterial endocarditis from a recurrence of a low grade rheumatic infection in a known subject of valvular disease may be very difficult. Joint and muscular pains, a minor pyrexia and embolic phenomena, with a sense of fatigue and exhaustion, are common to both and in each the illness tends to be protracted. Bacterial endocarditis can be diagnosed in these circumstances by the detection of albuminuria in an intermittent form, kidney involvement during the active phase of subacute rheumatism being most unusual, by the progressive development of a degree of anæmia out of all proportion to the fever, and by a greater impairment of nutrition with loss of weight, than that seen in uncomplicated rheumatism. The rheumatic patient is as a rule plumper, of a better colour and less toxic in appearance. The embolic phenomena of rheumatic heart disease are usually single episodes, often major in their distribution (*e.g.* brain or lungs) and in the great proportion are largely the accompaniment of auricular fibrillation—a most uncommon arrhythmia in subacute bacterial endocarditis. Finally, in the relief of pain and fever, intermittent courses of salicylates in doses as full as can be tolerated will usually produce convincing evidence of the part played by rheumatism.

Both diseases—subacute bacterial endocarditis and rheumatism in active form—may co-exist. Of our 40 patients rheumatic symptoms, taking the form of arthralgia, muscular pains in the limbs, or swollen joints, were present in 50 per cent. Horder (1909-10) noted active rheumatic symptoms in 66 of his 150 patients, and more recently Jones (1947) observed sudden fleeting rheumatic pains in half of his patients. In our experience rheumatic symptoms during the course of the illness, either before or during the administration of penicillin, are an unfavourable feature, being commonly associated with the early development of congestive heart failure. We believe that rheumatic symptoms signify an active rheumatic carditis which may well be the cause of death.

## THE RESPONSE TO PENICILLIN

The drug is administered at three-hourly intervals day and night by intramuscular injection, preferably in the gluteal regions. In emaciated patients the scapular muscles have occasionally been used. The continuous intramuscular drip employed in our earlier cases was abandoned on account of the occasional occurrence of sterile abscesses at the needle site. Patients requiring penicillin for weeks at a time preferred the transient discomfort of intermittent injections at regular intervals to the continued annoyance of a needle attached to the thigh.

It is useful to summarise briefly the findings put forward by Christie (1946, 1948) from his analysis of the results obtained at the various centres selected for this investigation. By keeping the total quantity of penicillin constant (5 mega units) and varying the period over which it was administered, it became evident from the study of the first group of 52 patients that the duration of treatment was more important than the total quantity (Table I). The figures are abstracted from Christie's (1948) tables :—

TABLE I

*Shows the Effect of Varying the Duration of Treatment, the Total Dose (5 Million Units) being kept Constant*

	Number Treated.	Died Other Causes.	Relapsed or Died Infected.	Cured.
1.0 mega unit for 5 days .	18	17 per cent.	83 per cent.	0
0.5 " " " 10 " .	16	25 " "	50 " "	25 per cent.
0.25 " " " 20 " .	18	34 " "	22 " "	44 " "

By extending the duration of the course of treatment and varying the daily dose, it became evident that heavier dosage was capable of producing better results (Table II).

TABLE II

*Shows that Larger Daily Doses in a Prolonged Course (28 Days) Produce Better Results*

	Number Treated.	Died with Infection Apparently [Controlled.	Relapsed or Died Infected.	Cured.
0.1 mega daily $\times 28$ .	17	24 per cent.	41 per cent.	35 per cent.
0.25 " " $\times 28$ .	83	36 " "	16 " "	48 " "
0.5 " " $\times 28$ .	58	38 " "	7 " "	55 " "

It therefore appeared that 500,000 units daily for a month would control the infection in about 90 per cent. of previously untreated patients. In spite of this, nearly 40 per cent. of the 58 patients died of heart failure or embolic episodes.

Some disquieting facts were, however, revealed. No good reason could be given for such relapses as did occur and in approximately one-third of the patients dying after apparently effective treatment, organisms, seemingly viable, were found in the heart valves on section. Furthermore, shortly after apparent cure of the infection a proportion of patients died from congestive heart failure. Further trials with the

same dosage conducted between April 1946 and January 1948 have confirmed these findings. Preliminary results are available on a small group of patients who received from 0.5 mega units up to 2 mega units daily for longer than twenty-eight days. Of these none relapsed or died with the infection uncontrolled. No less than 80 per cent. recovered and only 20 per cent. died (Christie, 1949). This suggests that the original method recommended ( $0.5 \times 28$ ) is too small and might be increased with advantage to a level which will eliminate the infection in all cases except those with an organism highly resistant. It is probable that 2,000,000 units a day for six weeks will satisfy these requirements.

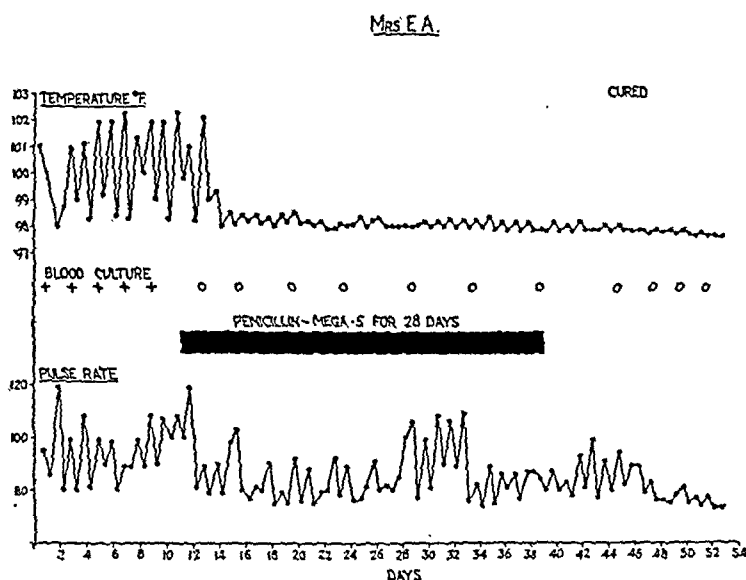


FIG. 4.—The temperature chart of a girl aged 21 who made a very satisfactory recovery. Her progress was uninterrupted. She had been feverish for three weeks before treatment and her blood yielded a succession of 5 cultures positive for *strept. viridans*. In this patient, as in others, there is often a lag in the temperature response to penicillin. Two or three days commonly elapse before the temperature falls. See also Fig. 3.

### ILLUSTRATIVE CASES

The response of the individual patient to penicillin is of considerable interest and may be illustrated by a typical temperature chart such as that presented in Fig. 4. This girl, aged 21, had a previous rheumatic history, mitral valvular disease, had had two teeth extracted four weeks before the development of incapacitating symptoms, headaches, malaise and joint pains. A swinging temperature of the type depicted had persisted for three weeks before treatment was commenced. Her nutrition was good, she had petechiæ on the chest and conjunctivæ and gave a succession of 5 positive blood cultures. B.S.R. 38-50 mm./hr., Hb. 70 per cent. Coefficient of resistance of *strept. viridans* 1. This girl made an uninterrupted recovery, had no embolic incidents during the recovery phase and was able to leave hospital fourteen days after completing her penicillin course. She was readmitted to

hospital two years later in another attack of rheumatic fever, from which she made a good recovery.

We have been struck by the lag in the temperature response to adequate doses of penicillin. This is shown in Figs. 3 and 4. Two to three days commonly elapse, during which the pyrexia persists before it finally settles. Indeed, the temperature is sometimes higher during the first two days of penicillin than previously. The patient, whose chart is depicted in Fig. 3, had her most severe rigor the evening before her temperature finally settled within the normal range.

A less satisfactory response is seen in Fig. 5. This boy, the subject of congenital heart disease (patent interventricular septum), aged 15,

D.M.

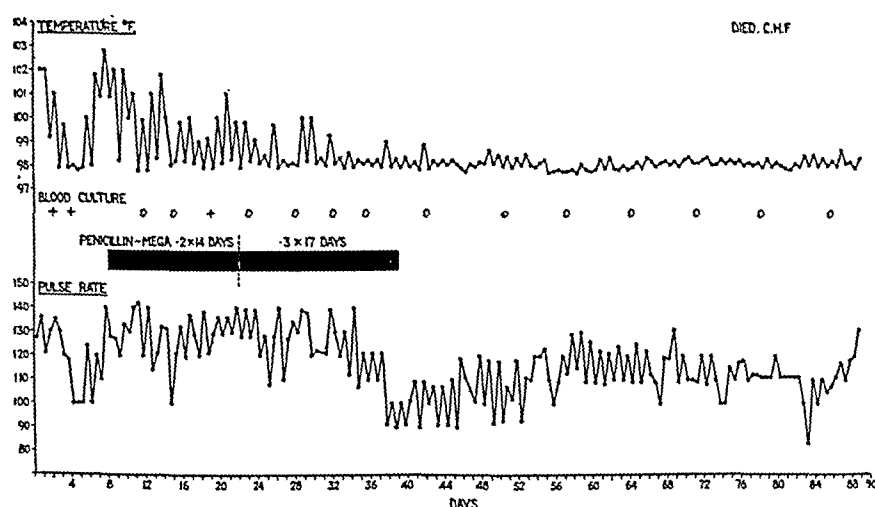


FIG. 5.—The temperature chart of a boy aged 15, the subject of congenital heart disease (patent interventricular septum). In contrast to Fig. 4 this is an unsatisfactory response: the pyrexia continued in a modified form despite the ultimate control of the infection. He died in congestive heart failure fifty-one days after completion of the course of penicillin. The augmented tachycardia observed during penicillin therapy was attributed to emotional causes.

a highly nervous and apprehensive youth, had an intermittent pyrexia, slowly subsiding over his thirty-one-day course. He never succeeded in adapting himself to the injections, which he dreaded as much at the end of the course as at the beginning. We attributed his tachycardia, which persisted during penicillin therapy, largely to this cause. One positive culture was obtained eleven days after commencing treatment. In spite of control of the infection, he developed congestive heart failure and died seven weeks after completion of his penicillin course.

Short courses of treatment are now known to be a grave mistake, as they are followed by a high relapse rate. Fig. 6 has been constructed from the temperature charts of a man aged 50 who had been ill for three months with evening temperature of  $102-103^{\circ}$  before the diagnosis

was established and penicillin commenced. He was treated in January 1945 with a short course ( $0.5 \text{ mega} \times 10$ ) but relapsed in nineteen days. The "flick" of temperature previous to the positive blood culture on the thirty-fourth day was preceded by joint pains and swelling of the right wrist. Thereafter his condition gradually deteriorated and penicillin was recommenced in a second course to which he responded on this second occasion. He has maintained good health since then. Relapse, when it does occur, is usually within one month of completing treatment.

The futility of short courses of penicillin is illustrated in Fig. 7. This girl, aged 15, had rheumatic aortic and mitral disease and had

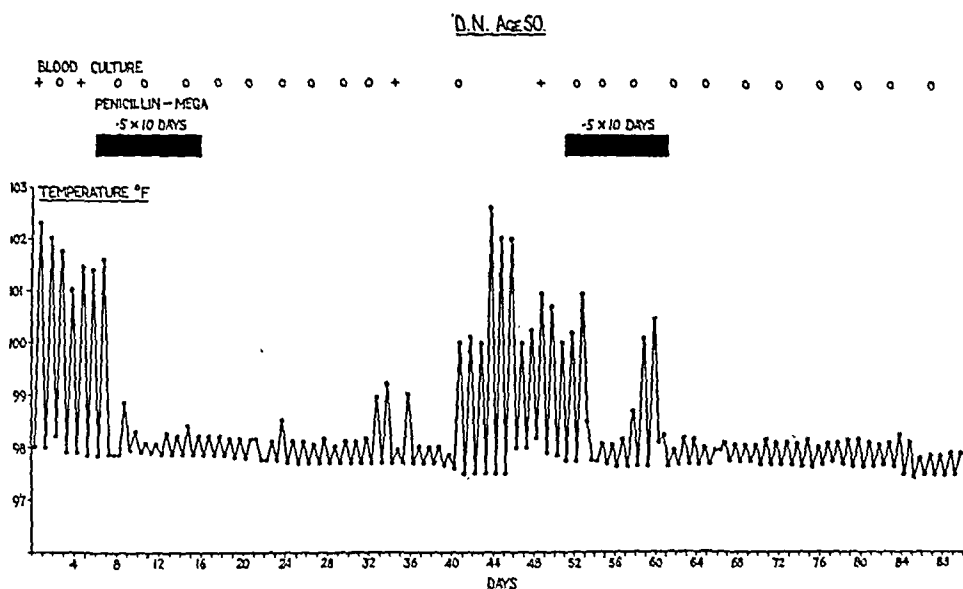


FIG. 6.—The temperature chart of a man aged 50, to show the occurrence of a relapse after a short course of penicillin. He had been ill for three months, with evening pyrexia, before coming under observation. The first indication of relapse was pain and swelling of the right wrist, followed by fever and a positive culture. Contrary to the rule, he responded to a second similar course and continues in good health four years after the attack.

been feverish at night for three weeks before coming under treatment. She was under observation in the hospital for fifty-one consecutive weeks. She relapsed on five occasions, but ultimately made a good recovery and is now back at work. The conclusion is justified, that if disappointments in treatment are to be avoided, a prolonged course of eight weeks should be advised in all who relapse, as it appears that those who relapse are slightly more resistant to subsequent courses. This girl developed during the first few days of observation a mycotic aneurysm palpable through the abdominal wall, which grew to the size of a small tangerine orange, probably involving the pancreaticoduodenal artery. By the time she left the hospital the aneurysm had shrunk in size to such an extent that it could not be recognised with certainty.

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## ANALYSIS OF RESULTS

Our experience is based on 40 cases of subacute bacterial endocarditis under observation from October 1944 to December 1948. We have also observed 3 cases of acute bacterial endocarditis and in the same period of time 6 patients with an infected pulmonary artery associated with a patent ductus have been treated with or without penicillin.

Confining our attention to the 40 cases of subacute bacterial endocarditis, it must be emphasised that only 31 of these received full and sufficient treatment, 3 patients dying within forty-eight hours

J.C.

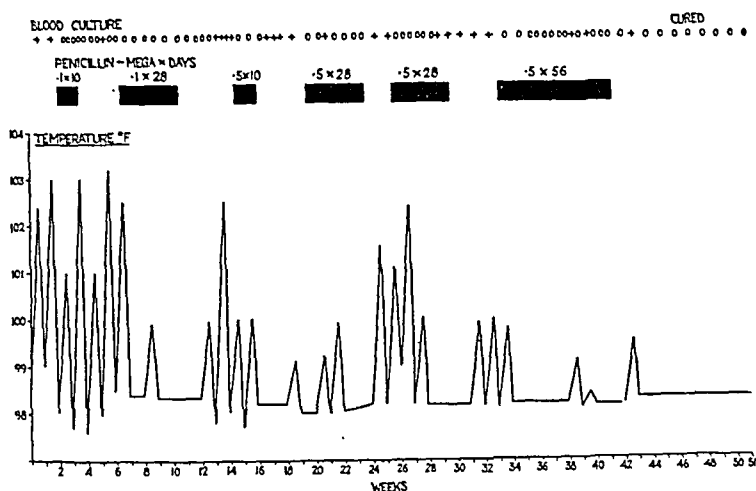


FIG. 7.—Temperature chart of a girl aged 15 who was under observation for fifty-one consecutive weeks. She relapsed on five occasions but ultimately recovered after a double course of 500,000 units daily for fifty-six days. This case illustrates the futility of short courses and the necessity for more prolonged treatment in those who relapse. Furthermore, a single positive culture was obtained three days after the completion of her last course but there were no supporting signs and the girl has kept in good health. It requires a *succession* of positive cultures to establish the diagnosis in the absence of other conclusive signs.

of admission to hospital. Of the 31 thoroughly treated, 21 survived and 10 died. Of the 40 patients, 19 were females and 21 males, and of the deaths 6 were females and 13 males—probably a significant distinction. The average age of the series was thirty years. The four oldest cases were fifty-seven, fifty, forty-seven and forty-seven years; all were males and all survived. The number of cases in which the infection was grafted on a rheumatic lesion was 36; in the remaining four a congenital flaw existed, the lesion being in two instances a ventricular septal defect and in two a pulmonary stenosis. We have no examples of subacute bacterial endocarditis in cyanotic congenital lesions nor of involvement of the tricuspid valve, despite



the comparative frequency with which it is affected by a rheumatic endocarditis (Coombs, 1924; Gilchrist and Lyon, 1933), presumably for the reason that the strept. viridans requires a high oxygen tension for its survival.

Of the 36 rheumatic cases the valvular lesions on which the infective process was superimposed were distributed as follows: mitral 13, aortic 5, mitral and aortic 18. There appeared to be no connection between the prognosis and the valve or valves affected, although Christie (1948) noted the highest mortality with the combined lesion.

### BLOOD CULTURES

Reference has already been made to the place of blood cultures in diagnosis. In this series 27 gave positive and reliable results and in 13 no organism could be demonstrated despite repeated endeavours. Of the 13 negative cases, 9 came to autopsy where the clinical diagnosis was fully substantiated. In the remaining 4 patients the clinical features and the response to penicillin left the diagnosis in no doubt. Resort to culture of the blood obtained by sternal puncture was made in a number of instances as Baserga and Barbagallo (1938) state that a higher incidence of positive information regarding the infecting organism can be obtained in this way as compared with the usual specimen of venous blood. In no instance in our series was an organism recovered from the sternal marrow when the usual blood culture was negative. We are unable to account for our series of negative cultures. They were obtained from a variety of patients in whom the disease was obviously active. We did not associate the negative culture with the "bacteria-free" stage described by Libman (1941) except in one instance. Fig. 3 demonstrates the temperature chart of a patient experiencing rigors in whom from successive cultures no organisms or contaminants of any kind were recovered. The other clinical features, dramatic response to penicillin and the post-mortem findings, left no doubt as to the diagnosis. A very strict technique has been employed in obtaining blood for bacteriological purposes. The details of the procedure are those advised by Shearer (1945).

To be of clinical significance more than one positive culture must be obtained. The unreliability of the recovery of a streptococcus from the blood on a single instance is illustrated by the fact that this organism was grown from 3 patients on isolated occasions at varying periods following the completion of penicillin treatment, when there was no clinical evidence then or subsequently to suggest relapse. A second confirmatory culture could not be obtained, indicating that the first was probably attributable to a transient bacteraemia, known to occur occasionally in health from time to time.

The colony count, that is the number of colonies of the organism obtained from a standard quantity of blood, after a given time, is often regarded as a rough measure of the grade of infection. We have

not found it of value in the management or assessment of the cases treated. A wide range of different figures can be obtained from cultures taken at intervals of five minutes and, indeed, from two specimens of blood withdrawn simultaneously from the right and left arms of the same patient. Furthermore, different laboratories report very divergent figures from samples of the same specimen of blood; Table III illustrates the wide range of figures.

TABLE III

*Shows Difference in the Colony Count on Identical Specimens of Blood Drawn from the Same Patient*

		Colonies per c.c. of Blood.	
		Zero Time.	Zero + 5 Minutes.
Laboratory No. 1	.	117	317
Laboratory No. 2	.	3	0

The sensitivity of the organism to penicillin should be determined quantitatively, the result being expressed as its coefficient of resistance. Christie's (1946, 1948) analysis indicated that the "percentage of patients who relapsed or died with the infection uncontrolled did not appear to be affected by the resistance of the organism over a considerable range." It is known that crude penicillin varies in its content of the four varieties, F, G, X and K, of which it is composed. Penicillin G is the most influential in overcoming strept. viridans and we consider that in determining the coefficient of resistance of the organism perhaps a better correlation between the bacteriological findings and the clinical response might be obtained in future by using the same penicillin for the determination of the coefficient of resistance as employed in the treatment of the particular patient. The introduction of pure crystalline penicillin G may be an advantage for the determination of the coefficient but our clinical impression is that in the early days of penicillin, when the preparation then in use was crudest of all, the response to treatment was more favourable. Five deaths occurred in our first 20 patients, when the penicillin used was less refined, and 14 deaths in the second 20, despite the fact that the second series had longer courses and heavier daily dosage. Support for this view is substantiated by the admission of one manufacturer that during the period June to October 1946 their product contained an excess of penicillin K, thus lessening the proportion of penicillin G—the more important component in the extermination of the strept. viridans. Christie (1948) concludes that when the coefficient of resistance exceeds 8 or 10, the course of treatment should be more prolonged and with a daily dose greater than the standard 0.5 mega units.

#### ANALYSIS OF CAUSES OF DEATH

In the pre-penicillin era approximately 35 per cent. of patients suffering from subacute bacterial endocarditis died of cachexia, as the

accompanying analysis of 65 cases examined post mortem during the ten-year period 1934-43 in the Royal Infirmary demonstrates (Table IV).

TABLE IV

*Shows cause of Death in Subacute Bacterial Endocarditis*

	Cachexia.	Congestive Heart Failure.	Embolism.	Uræmia.	Others
Pre-penicillin deaths (65 cases).	35 per cent.	34 per cent.	23 per cent.	3 per cent.	5 per cent.
Penicillin deaths (19 cases : this series).	0	43 " "	43 " "	0	14 " "

It appears that cachexia as a cause of death can be effectively overcome by the use of penicillin, but it is difficult to offer an entirely adequate explanation for the apparent increase in the deaths from embolism in the present series. Eight of 19 patients died from this cause, but it seemed probable that 4 of these might have died later from congestive failure had they not already succumbed to a major embolus. Our figures are too small to permit of a strict comparison between the two groups.

Death from congestive failure is now a much greater hazard to the patient than the risk of failure to overcome the infection. This increase in congestive heart failure deaths requires the closest attention. It is discouraging to see the patient overcome the bacterial infection only to die from congestive heart failure, refractory to all the usual therapeutic measures. The explanation that the high figure for deaths from congestive failure arises as a result of control of cachexia, which would otherwise prove fatal, is not substantiated by the facts. There appears to be no relationship between the two conditions in this series of patients. Those who were most cachectic and were cured by penicillin did not develop congestive heart failure.

Rosenblatt and Loewe (1945) have described cases in which a degree of valvular damage and distortion never previously encountered in the pre-penicillin era was found at post mortem shortly after the end of a course of penicillin. The healing process had reduced the aortic cusps to stumps which must have been almost functionless. A tremendous strain must thus have been imposed upon the heart. Bloomfield (1945) has made similar observations at autopsy in fully treated cases. This distortion and structural damage has not been seen in any of our 8 cases who died in heart failure shortly after a successful eradication of the infection by penicillin. Indeed, a "mechanical" cause for the development of congestive heart failure is exceptional. The streptococcus viridans has few invasive properties and the pathological process is for the most part superficial, but exceptions occur. One patient, for example, developed abruptly a large perforation of an aortic cusp (Fig. 8) and in another patient an aortic sinus ruptured, as suddenly, into the right ventricle (Fig. 9). In each of these instances the intense mechanical burden thrown precipitately on the heart muscle led to the rapid development of congestive failure and death within a few days.



FIG. 8.—Photograph to show two ruptured aortic cusps in the heart of a man aged 34 dying of acute left ventricular failure after an illness of nine weeks' duration. The abrupt alteration in circulatory dynamics, in consequence of the free aortic regurgitation, was the immediate cause of death. The perforations in the cusps had fresh, red, friable vegetations.





FIG. 9.—Photograph of the heart of a man aged 26 who suddenly developed while under observation a loud continuous murmur, exactly similar in quality to that of a patent ductus, though more superficial and heard over the lower sternum, being maximum at the third left interspace. He died eight days later in advanced congestive failure, developing rapidly after the establishment of the fistula, and apparently a direct result of the mechanical handicap abruptly imposed on the ventricles. At autopsy large vegetations involved an aortic sinus from which a channel extended into the conus of the right ventricle. A marker has been placed in the perforation to show the path of the arterio-venous fistula. The subject of intracardiac fistulae has recently been reviewed by Taussig (1947) and by Herrmann and Schofield (1947).

is evidence to suggest that larger daily doses (up to 2,000,000 units) for a longer period of time (six weeks) may eradicate the infection even more completely, with less risk of relapse and with a further reduction in the mortality rate.

(3) Difficulties in diagnosis are discussed. Negative blood cultures (recorded in 32 per cent. of our patients) do not exclude the disease. Pyrexia, in a cardiac patient, of ten-days' duration, in the absence of any obvious cause, should always suggest the diagnosis, which becomes even more probable with a history of dental extractions within the preceding few weeks. In diagnosis the importance of the minor embolic manifestations in the skin, fingertips, conjunctivæ, retinæ and urine cannot be over-emphasised.

(4) Early recognition will reduce the mortality rate further, but deaths from emboli and from congestive failure are bound to occur. Allowing for these, the recovery rate may yet amount to 80 per cent. or more.

(5) In our experience frank rheumatic symptoms during the course of the illness are an unfavourable prognostic sign. They commonly signify the subsequent development of congestive heart failure, which often proves fatal. We believe that in the majority of instances the congestive failure observed in subacute bacterial endocarditis arises largely as a result of an active or reactivated rheumatic myocarditis.

(6) Subacute bacterial endocarditis may now be regarded as a surface infection, which leads to death from embolism.

(7) It is possible to prevent and cure bacterial endocarditis. It remains to prevent and cure its common associate, acute rheumatic carditis, which leads to death from congestive failure.

To the Physicians of the Royal Infirmary who placed their patients under our care we express our grateful thanks for their most helpful co-operation. We are also indebted to Professor T. J. Mackie and Professor A. M. Drennan for bacteriological and pathological facilities, and particularly to Professor J. R. Learmonth for much help and guidance in the early days of penicillin treatment. Professor R. V. Christie has kindly supplied us with some recent and unpublished data.

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## DISCUSSION

*Dr W. A. Alexander*, opening the discussion, said that he hoped that in the future, as in the past few years, a special team would accept responsibility for the management of these cases, which require such prolonged and thorough treatment.

He recalled a type of case which had been seen after the first world war but not to the same extent after the recent war. It was generally accepted in the belligerent countries of the first world war that there was an increase in the incidence of subacute bacterial endocarditis and that this was due to the occurrence of the disease in men who had been through the rigours of war. It was noticeable here. *Dr Alexander* said he had been working in the pathology department then and, on looking up the records for the year 1920, he found that there were 12 cases at post mortem which could be accepted as examples of subacute bacterial endocarditis. Eleven of these cases were in males and, though he could not give exact details, he knew that a considerable number had been through the trenches. Most of these showed the aortic valve to be affected. Some had bicuspid aortic valves, a feature later emphasised by Lewis and Grant who came to the conclusion that this was really a congenital anomaly, but in others there was no convincing evidence either of congenital defect or of antecedent disease, and he thought that there was some justification for claiming that the stresses of active service were in part responsible.

*Dr Gibbs* expressed his gratitude and that of the dental department for the help they received from *Dr Gilchrist* and his workers. This help consisted of lines of thought suggested to them which in themselves had suggested treatment which had quite revolutionised the ultimate results of certain dental conditions.

It had occurred to him that the question of relapse of certain cases of bacterial endocarditis might be due to the fact that the mandible which had been the seat of the advanced paro-dental lesions might act as a reservoir of streptococcus viridans. In investigations of many of his cases of advanced paro-dental lesions he had found streptococcus viridans active in the mandible for as many as nine years after the extraction of the teeth.

*Dr Douglas Robertson* said that he was impressed by the important rôle played by dental extraction in the etiology of subacute bacterial endocarditis. Was it not advisable that all persons suffering from organic cardiac disease should be adequately treated with penicillin before and after dental extractions? Many cases of subacute bacterial endocarditis might be prevented if this were done as a routine practice.

*Dr Gilchrist*, in replying, expressed the opinion that one explanation for the absence of the very chronic cases of bacterial endocarditis—endocarditis lenta—in the years following the most recent war, might be found in the fact that with the employment of stricter standards for recruitment fewer men were admitted to the services with even minor degrees of chronic valvular disease than in the 1914 war. Coupled with this was the fact that so far as the British Army was concerned, better standards of dental care were observed during the recent campaigns and therefore the likelihood of this source of infection was probably greatly reduced in that there were also fewer candidates for the disease.

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# Edinburgh Medical Journal

*April 1949*

## SOME FUNCTIONAL NERVOUS DISORDERS IN CHILDHOOD

By J. L. HENDERSON, M.D., F.R.C.P.E.

I MUCH appreciate the compliment of an invitation from the Clinical Club to give a talk on a pædiatric subject. I have chosen to speak to you about some of the commoner functional nervous disorders of childhood, because I believe children suffering from such disorders constitute a considerable proportion of a family doctor's juvenile patients. Moreover, I am particularly interested in these disorders, not only because I am a pædiatrician, but also because I myself experienced a variety of them in childhood.

There is often a difference of opinion about the relative influence of heredity and environment in functional nervous disorders. I believe heredity is the dominant influence in the causation of functional nervous disorders in childhood, since it not only determines the child's constitution, but also that of the parents and siblings who are the major influence in the child's small world. With increasing years the influence of the family environment diminishes, though it always remains strong, and the influence of the outside world progressively increases by virtue of the child's ever widening horizon.

### FEEDING PROBLEMS

Feeding problems are a common form of behaviour disturbance and probably cause more anxiety, and exasperation, in the parents, than any other functional nervous disorder in childhood. They strain the mother-child link to the utmost and often predispose to other emotional disturbances, such as sucking habits, while malnutrition is a common sequel. Most feeding problems begin in the first two years of life. They are almost always caused by a lack of knowledge of infant management coupled with maternal over-anxiety and, therefore, most often arise in first children.

Inexperienced mothers with their first baby often show great concern because the baby falls asleep after five or ten minutes at the breast, instead of feeding for twenty minutes as advised by the doctor, or, if bottle-fed, because he does not finish the feeds recommended. Instead of the mother being pleased and happy like the child, who is blissfully satisfied, she is anxious, imagines the child to be underfed,

An Address to the Edinburgh Clinical Club given on 17th February 1949.

and attempts to waken him. When he opens his mouth in protest she reinserts the nipple. Repeated attempts to compel the child to take more than he needs, and as much as the mother mistakenly believes he should have, must be, and are, very frustrating to an infant who knows his own business. Persistence of such tactics soon causes loss of appetite which is the pleasurable anticipation of food. Instead of being entirely pleasurable and terminating with a blissful feeling of satiety and contentment meal times become an unpleasant experience terminating in a conflict. Spock (1945) truly says: "If a child has been systematically robbed of his desire for food from the very outset, the mother may be quite truthful when she reports that the child, now five years old, has never shown any appetite."

During the last fifty years infant feeding has been dominated by the idea of caloric requirements and extreme regularity, perhaps a natural development in a scientific age, but one which ignores the fact that until the twentieth century the young of the entire human race, like the young of other mammals, always determined their own feeding time and took as much as they wanted without disastrous results. The view is spreading that insistence on rigid routine ignores the variations in functional capacity of individual babies, and creates frustration in those who have difficulty in conforming to the routine. We know that some infants and young children, like adults, require twice as much food as others, while some require almost twice as many feeds per day. Not only were feeding problems encouraged in young children by such unphysiological conceptions, but mothers also suffered through being encouraged to become tense, intolerant, and authoritative in their attitude towards their children. It is surely ironical that those uninfluenced by scientific dogma and fashions in infant dietetics, the stable instinctively good mothers everywhere, should, by virtue of the blessed gift of common sense, have been feeding their children on more sound biological lines than many of those who have professed to guide them.

Much of my knowledge of the physiology and management of feeding in infancy and early childhood has been acquired in the best possible circumstances, in my own home. My experience with my three children has greatly liberalised my conception of feeding management and simplified my teaching. In my earlier teaching days I took unnecessary pains to calculate what was generally regarded as the correct number of calories a child should have and insisted on punctual feeding. Now, I find infant feeding so much simpler, for, having given instructions about the character and strength of the feeds, I say to a mother: "Give him as much as he wants, but do not try, after he ceases to be eager, to give him any more, for he is the best judge of the amount he needs at each meal. Moreover, adjust the feeding times, which should be about — in number, to suit the convenience of baby and yourself, but be as regular as such circumstances will allow. If he wakes at 2 a.m. and will not settle without

a feed, feed him ; all babies will give up night feeds as soon as enough is being taken at the other meals to allow them to sleep throughout the night. Some mothers fear the establishment of a habit of night-feeding by so doing, but this is groundless, for in a few weeks it will no longer be desired." I have found that small babies with a birth weight of 5 to 6½ lbs. often demand a night feed in the early weeks of life.

Feeding problems more often commence when solid foods are first introduced than in younger infants, but they most often begin about the age of one year. Most babies are doubtful about the first few mouthfuls of solid food ; many look bewildered, some disgusted, and ejection of the food is common. After all, the consistence, the taste, and the spoon are all strange. Most babies will take a little solid food after two or three days and become enthusiastic within a week or two. Others show increasing dislike with each day and persistence will be rewarded only by mounting obstinacy. If such a struggle is persisted in for two or three weeks the child may not only refuse his cereal, but his milk also, because his resistance has been thoroughly aroused and has spread to other forms of food. To avoid the development of such a feeding problem the mother must feel her way cautiously when introducing solid food. Education of the palate is the main objective and the amount taken of little importance. Once eagerness is shown the amount can be increased quite quickly. Cereal is so often disliked at first that some advise the inauguration of solid feeding with fruit, such as apple-sauce or mashed banana, since it is nearly always well received (Spock and Huschka, 1938). Once enthusiastic about solid food in such a form the child becomes uncritical and will usually take any form of solid food without ado, aye with avidity, during the remainder of the first year. After the age of one year increasing egotism and negativism are responsible for unpredictable variations in appetite and choice of food. Moreover, the child begins to feed himself at this age. Many mothers who do not appreciate these normal characteristics of the second year become distressed about the child's fickleness over the kind and amount of food he eats, and by his touchiness over the manner of feeding. The child is coaxed and even forced to eat and his obstinacy increases if he is a child of character. Mother and child are then at loggerheads over feeding and become disillusioned in one another.

The foods most often refused, or taken in reduced amount, at this age are vegetables, cereals, and milk. Intelligent handling, with patience and courage, are important at this period, and alternatives must be freely used in the diet to avoid building up resistance against any form of food, particularly the staples—cereals, milk, and vegetables. The child must continue to think of food as something always to be enjoyed and must not be made to feel that any foods are his enemies.

Feeding problems occasionally commence after an illness. An over-anxious mother, eager to hasten the period of convalescence,



may force food too soon before the appetite returns. The forcing of food in face of the anorexia following illness quickly creates an intense disgust, more permanent than forcing food in health. The mother must be patient and wait for the appetite in these circumstances, and its natural return will soon repair the effects of illness without the intervention of any unpleasant experiences or feeling of disgust towards any form of food.

The treatment of feeding problems is usually a slow process requiring regular supervision by the doctor. The parents' fear that the child will starve to death must be convincingly repudiated, and the parents should be warned to expect a decrease of food intake and a fall in weight at the beginning of treatment. If the child is old enough it may be desirable for the anxious parent not to be present at meal-times. The food should be served in an appetising way and casually removed after a reasonable period, thus implying that the child has eaten all he desires. It is often effective to serve the food in very small helpings to encourage the child to think—"Is that all?"—instead of in large helpings, when the reaction is likely to be—"Must I eat all that?"

A feeding-problem child must be allowed to eat or leave any food without discrimination, for he must be encouraged to think of food as something he wants, and not as something others want him to take. Clara Davis (1928) showed that when young children are allowed to select their diet from a large number of alternatives placed before them, the selected foods, though varying from time to time and as between one child and another, always provide a well-balanced diet. The fancy for the foods we need remains with us throughout life. Improper management in respects other than feeding should be looked for in every case and adjusted, and any causes of anxiety and tension in the home removed.

I have considered feeding problems at some length because they are so often encountered in general practice. Unhappy is the home where there exists a full-blown, persistent feeding problem betwixt a mother and her child. In such circumstances the psychological implications are so complex that the assistance of a child psychiatrist may be desirable. *Feeding Our Old-Fashioned Children*, by Professor and Mrs Aldrich (1941), is a well-balanced account in simple language of feeding management in early childhood.

### SUCKING HABITS

Sucking of the fingers occurs at some time in nearly every child's life. Many infants suck their fingers only when hungry, others derive pleasure from it. Occasionally the toes are sucked, whilst the sucking of some object, such as a garment, is common, and often preferred to a digit. Associated movements, such as twisting the hair, pulling an ear, or rubbing some soft fabric, often occur, and may persist after the sucking has ceased, or may even be a substitute for it. These

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associated movements are considered by some to be residuals of fondling the mother during nursing. Handling the genitals is another form of associated movement; this is usually called infantile masturbation, a misleading term of which I disapprove, since this infantile pleasure reaction is not sexual in the sense applied to adult sexual reactions. Whether the object of choice is a digit, one of a great variety of objects, or some associated movement, there is absolute constancy in the object of the infant's or young child's choice after the age of about six months, and no substitute is tolerated.

The most important aspect of sucking habits is parental concern, much of which has arisen since the beginning of this century as a result of alarmists' warnings. Langford (1939) in a good paper on sucking habits in childhood, read at the annual meeting of the American Academy of Pediatrics, remarked: "If the habit is so harmful why is the alarm so recent?" The harmful effect of finger sucking on the conformation of the palate and dental arches has been stressed by various observers, and many other ill effects have been alleged. Such disquiet has produced a great variety of ways and means of trying to curb the habit. A variety of mechanical devices on the arms or teeth, and drugs on the fingers have had their advocates, but all these, like constant nagging, serve only to focus the child's attention on the habit. Such measures have only a temporary effect, are most often successful during infancy, and are definitely harmful after the first year.

Deformities of the mouth, with mal-occlusion, may be caused by finger sucking, but if the sucking is discontinued before the eruption of the permanent teeth the deformity will spontaneously disappear, like most acquired deformities in childhood, once the exciting cause is removed. Johnson (1939) in a series of 989 cases of mal-occlusion in childhood, found that  $17\frac{1}{2}$  per cent. of the children were habitual thumb-suckers or finger-suckers; some investigators have found a higher incidence; Hellman (1929), for instance, had an incidence of 29 per cent. in 354 cases, but unlike Johnson he included lip-suckers and tongue-suckers. Habitual sucking has been blamed for a great variety of physical disorders including scoliosis, diseased tonsils and adenoids and digestive disturbances, but there is little, if any, foundation for such beliefs.

Sucking is an infantile pleasurable reaction, and it would seem that the child who resorts to such a purely infantile form of satisfaction is being deprived of adequate satisfaction in life. The significance of sucking varies with the age of the child. There are three distinctive age groups: (1) the infant; (2) the toddler and pre-school child; (3) the school child. I shall now discuss these groups in more detail.

(1) THE INFANT.—The newborn infant will suck reflexly almost any object which contacts his lips. This reflex sucking persists for the first few months of life, but a well-fed infant has little inclination to suck for pleasure at this age. From the fourth to the tenth month of life—"The hand to mouth reaction period"—the infant uses the

tactile sensations in his lips and mouth as a means of exploring his environment. The tendency to convey objects to the mouth is greatest during the eruption of teeth and may almost completely disappear in between. Levy (1937) has emphasised that sucking is encouraged, in the majority of cases, by either incomplete satisfaction of sucking needs, by giving unduly short feeds, or by hunger due to underfeeding; and Gesell and Ilg (1937) have pointed out that the sucking needs of infants vary greatly. Some can discontinue bottle feeding at five or six months without developing abnormal sucking responses, while others equally well-fed and contented are unwilling to give up sucking experiences until after the first birthday. Clearly, then, occasional finger sucking should not be regarded as abnormal in the first year, but if sucking occupies much of an infant's time, when awake, it signifies that he is not getting all the satisfaction from life that he needs. A change in the technique of feeding, or in the type of food, to make feeding a more satisfying experience, and perhaps more mothering, may be all the treatment that is needed.

(2) THE TODDLER AND PRE-SCHOOL CHILD.—In children aged from one to five years there are a variety of causes of finger sucking. Boredom tempts young children to derive pleasure from sucking habits. We are apt to forget that the attention span of toddlers is brief, and that one type of play, or one or two toys, will hold a child's attention for only a brief period. Punishment and frustration, often in the form of unreasonable nagging or snubbing, often induce a sucking response in toddlers as a source of pleasure and comfort. The child of three or four years who normally exhibits much curiosity and uncontrolled activity is subject to many frustrations, and transient phases of the sucking response are the rule rather than the exception at this age. Excessive frustration may induce habitual sucking and the child may seem completely entranced and oblivious of his surroundings: such children are usually mismanaged and misunderstood and have little opportunity of normally satisfying emotional experiences. Tired and physically ill children also tend to suck their fingers; most young children indulge in sucking at bedtime and solace themselves to sleep. With few exceptions, then, sucking responses in the pre-school child are of minor significance, and represent a reasonable regression to the earliest pleasure pattern. They require only to be understood to be intelligently handled. When the underlying causes of sucking—fatigue, sleepiness, emotional dissatisfaction—are removed, there ceases to be any reason for it and it disappears. A direct attack on the habit is not only unnecessary, it is harmful, for then another frustration is added to the child who is unable to give up the habit because of the persistence of the underlying causes.

(3) THE SCHOOL CHILD.—Sucking is uncommon after five years of age. In the school child sucking is a more serious disturbance for it is a manifestation of a more general emotional and social immaturity, which, if neglected, may lead to a serious and lasting personality

disorder. Moreover, there is now a danger of permanent deformity of the palate and teeth. A variety of circumstances may cause the disturbance in the school child. The commencement of school life puts a great strain on the nervous system of many children and functional nervous disorders are common at this time. The over-protected child of indulgent parents, and the only child, are particularly apt to find adjustment to school life difficult. Management of sucking habits and associated nervous disorders at this period involves a thorough investigation of the underlying causes of the abnormal behaviour with environmental and personal readjustment.

### BOWEL AND BLADDER TRAINING

There is a growing and well-founded belief that premature and drastic toilet training are often important contributory factors in the development of emotional disturbances in both children and adults. In the histories of problem children there is a high incidence of serious emotional reaction to excessively early or rigorous toilet training. Voluntary bowel evacuation and micturition involves a degree of muscular and mental control and co-ordination quite beyond the capacity of any infant, yet training is often enthusiastically commenced at the age of a few weeks. Many mothers proudly assert that their baby never soiled a napkin after the age of a few weeks or months. Such babies are not trained, but their mothers are, for they have soon learned to anticipate reflex evacuation of the bowels after feeding, or on wakening, to avoid washing dirty napkins. The baby obliges quite involuntarily though most mothers would indignantly disagree. This practice of anticipating reflex evacuation is commendable, provided the mother shows no insistence and the infant no resistance. It may lead to the formation of a conditioned reflex, which is an involuntary act, but there is still no training in the voluntary sense. Premature or over-active training, which implies a sustained attempt to obtain co-operation, may cause severe tension between mother and child which may be the origin of maladjustment throughout life. The fashion of early training has also had a harmful effect on some mothers, for disappointment with the results of training engenders a sense of failure, and the development of defiance in the child hurts the mother's pride.

Training should not be commenced until a child begins to make his toilet wants known, thereby showing his psychological readiness to accept training. Mothers quickly learn the significance of signs such as grunting, wriggling, putting a hand to the genitals, or a slight flushing of the face. Infants are usually over the age of fifteen months before they signify their toilet wants, though some do so as early as eight months. The deferment of training until a child is physically and mentally mature enough to co-operate ensures that the training will be accomplished more quickly and smoothly, and will be much more likely to be permanent, since it results from psychological mechanisms evolving naturally within the child rather than from

external pressure. The age at which training is completed varies greatly. Many have attained complete bowel control and bladder control by day at the age of one and a half years, but some apparently normal children are a good deal older.

The method of training is more important than the age of its commencement. It should be conducted in a calm atmosphere of affection and mutual confidence. Unpleasant emotional impressions must never be associated with it. Displeasure on failure should never be expressed, while moderate praise for success is encouraging. When a child of the appropriate age resents training the mother should desist for a period until he is ready to accept it.

### TEMPER TANTRUMS

Children who display temper tantrums usually have a history of earlier behaviour disorders such as feeding difficulties and difficulties with toilet training. Tantrums are important because, if badly managed, they may lead to more serious neurotic manifestations. They constitute a clear warning that there is some maladjustment between parent and child which should, if possible, be eliminated. Tantrums often begin between the ages of one and four years. Occasional tantrums at this age are normal, since a large proportion of children have at least a few. If numerous, they may persist up to the age of ten years. They are commoner in highly strung children and those who are tired or ill. They may be caused by a great variety of situations, but are usually caused by trying to make a child do something against his will, or making him feel jealous by depriving him of something. The child reacts by aggressive activity against himself, his only solution short of capitulation. If he gains his desire by arousing pity, or exhausting his parent into surrender, he may learn to use the tantrum with increasing deliberation and purpose.

Treatment of tantrums consists of teaching the parents to avoid situations which provoke the child without allowing him to gain any unreasonable advantages or supremacy. The mother should be made to understand that they are a potential threat to the child's development towards normal adulthood and not merely a threat to her.

### HYSTERICAL APNŒA (BREATH HOLDING)

This interesting manifestation of emotional instability is closely related to temper tantrums, but is even more dramatic and alarming. I have seen many cases at the Medical Out-Patient Department of the Sick Children's Hospital and have become particularly interested in the disorder, which, I have found, is often misunderstood. On analysing the notes of 15 cases seen by me in this hospital I found that 10 of the children were boys, and that the age of onset was often about ten months, though it ranged from eight months to two and a quarter years. The attacks occurred at irregular intervals of a few

days to a few months. In every case each attack was always preceded by bitter crying, usually induced by frustration, but occasionally by pain following a fall or a knock, or by fright. The sequence of events is then uniform in this disorder. After a short period of great agitation and bitter crying breathing ceases and progressive cyanosis ensues. Then the child becomes unconscious, stares vacantly and stiffens up. Within a short time of losing consciousness, probably less than half to one minute, the child recommences to breathe, loses the cyanosis, and becomes very pale and limp. The child then usually falls asleep and wakens in an hour or two looking as if nothing unusual had happened.

In one of the 15 cases there was a history on two occasions of the typical tonic type of seizure giving way to a clonic type of seizure. This unusual feature may have been caused by unduly prolonged anoxæmia or an epileptogenic constitution, probably the former, since prolonged anoxæmia may cause convulsive seizures.

I think hysterical apnœa is a better term for this condition than the conventional one of "breath holding," because the cessation of breathing is involuntary, a hysterical loss of function. There can be no question of laryngeal spasm playing a part, because stridor does not occur and there is no attempt to breathe during the apnœic phase. The doctors of half of the referred cases regarded the condition as probably epileptic. The history of a nervous type of child who may have a history of other forms of behaviour disorder, bitter crying at the outset of each attack, respiratory failure, increasing cyanosis, and loss of consciousness with a tonic muscular spasm, followed within a minute by a return of breathing, loss of cyanosis, limpness, and a return of consciousness, should make the diagnosis clear.

In hospital one sees only the worst cases of hysterical apnœa. Undoubtedly, seizures occur in only a small proportion of attacks, because breathing is usually restored before that stage is reached, and most children with the condition never have any seizures at all.

The management of this condition is the same as in temper tantrums, since the aetiology is similar. The nature of the condition must always be carefully explained to parents who become desperately agitated and think death imminent when seizures occur.

### FUNCTIONAL VOMITING

**PSYCHOGENIC VOMITING.**—This is common in childhood. There is often a history of early emotional disturbance caused by feeding difficulties, and it is usually accompanied by other symptoms of emotional maladjustment. Common associated symptoms are excessive irritability and over-activity, fears, sibling jealousy, and over-dependence on parents. When no physical cause for vomiting in a child can be discovered the possibility of a psychogenic cause should always be considered. Such vomiting is not a response to any particular type of emotional problem, but a symptomatic response to any one, or several,



of almost an endless number of psychological situations. Frustration is a common cause. A child who dislikes school may vomit in the mornings, or it may be induced by an anxious mother's attempts at over-feeding. Vomiting usually enables a child to gain its objective. Treatment consists of completely ignoring the vomiting, if one can ignore vomiting, and attempting to remove the psychological causes by appropriate personal and environmental readjustment.

**RECURRENT FUNCTIONAL VOMITING AND REGURGITATION IN INFANCY.**—This type of vomiting and regurgitation, formerly believed to be caused by pyloric spasm, is now regarded as a local manifestation of psycho-muscular hypertonia. A high percentage of infants with this condition are females. They are highly-strung, lively babies who tend to be unduly wakeful and fretful. They have a keen appetite in keeping with their hyperactivity. The vomiting usually begins within a few days of birth. It occurs from 1 to 3 times a day, with periodic intermissions of a day or two, and it usually persists until mixed feeding is established at five to eight months. It does not appear to be voluntary. There is no constipation, as in pyloric stenosis, and the weight rises slowly.

Treatment consists of sedation, to diminish the abnormal mental and physical activity, and thickening of the feeds. Chloral gr. 1 to 2 before each feed is often helpful, also phenobarbitone gr.  $\frac{1}{4}$  t.d.s. It is often beneficial to thicken the feeds with a cereal such as corn-flour, or a partly dextrinised cereal such as Benger's Food, when the baby is bottle fed. An antispasmodic such as eumydrin mgm.  $\frac{1}{4}$  to  $\frac{1}{2}$  twenty minutes before feeds, in combination with the sedative, sometimes appears to be beneficial. Breast feeding should not be discontinued, unless the vomiting is severe and the child's progress unsatisfactory. In such circumstances weaning and the substitution of thickened feeds usually leads to improvement. It is desirable to give small feeds which entails increasing the number of feeds per day to 6 or 7. Such measures are likely to reduce the frequency of the vomiting, but, though the condition may subside at any time, it frequently persists in its ameliorated form until more solid food is being taken. The nature and benignity of the condition should be explained to the mother, whose chief concern will then become the smell of vomitus on the infant's clothes. She should be advised to express no concern and to be quite calm in her management of such a temperamental infant.

**RUMINATION.**—In this uncommon disorder, which is usually seen in the second six months of life, gastric contents are voluntarily returned to the mouth where they are chewed and played with before being swallowed again. Infants appear to derive great pleasure from the habit which is greatly encouraged by boredom. The regurgitation may be assisted by jaw movements, or putting a hand in the mouth. Some of the gastric contents are usually lost in this way, and the loss may be severe enough to cause a rapid loss of weight. Death has been known to occur from starvation. Rumination, like recurrent functional

vomiting in younger infants, occurs in the nervous, restless type of child.

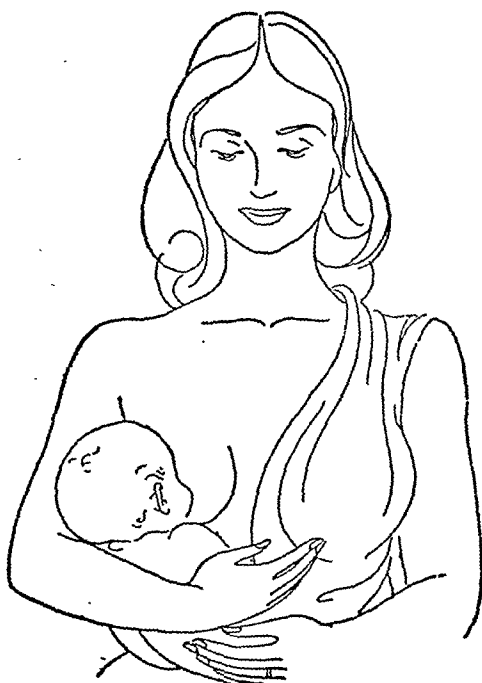
The habit of rumination may be difficult to cure. Treatment should be directed towards the elimination of conditions which foster boredom. This entails occupying the child's attention until sleep intervenes. Sedation may be a useful ally in a lively, wakeful child.

RECURRENT ACIDOSIS (CYCLIC VOMITING).—The term acidosis is popularly and loosely used, like teething and neurosis, when the nature of a disease is obscure. Acidosis is a regular consequence of starvation, whether caused by illness or anorexia. Recurrent acidosis, in which I have been particularly interested, is a common syndrome of childhood with characteristic features. Vomiting occurs in severe attacks of acidosis, in which it constitutes the outstanding feature, hence the synonyms recurrent vomiting and cyclic vomiting. The disease has often been regarded in the past as primarily a metabolic disorder, particularly of fat metabolism, but experience has left no doubt in my mind that the condition is fundamentally a functional nervous disorder. An important contribution to our knowledge of the disease has recently been made by a general practitioner, Dr King of Fallin, Stirlingshire, who submitted an M.D. thesis to the University of Edinburgh in 1947 entitled *Observations on Recurrent Vomiting with Acetonuria in Children*. Dr King's field study on the clinical aspects of the disease, conducted over a period of fourteen years in his rural and mining-village practice, is particularly valuable because he has studied the life history of his patients, and observed the disease at all ages, at all stages of the characteristic attack, and in attacks of every degree. Most of the literature is based, like my own experience, on patients seen in hospital and consulting practice, and thus gives an unbalanced picture, since the data are largely based on histories, severe attacks, and the full-blown and later stages of attacks of the disease.

Dr King observed 36 children who suffered from attacks of recurrent vomiting which recurred after varying intervals. He observed 133 distinct attacks in these 36 children who showed a low incidence of other complaints common in childhood. I am sure many of you are aware that recurrent acidosis only occurs in children of a certain physical and mental type, but I would like to quote King's description of the general characteristics of these patients. "These children always have a characteristic appearance. They are small and pale, with bright eyes and red lips, thin and nervous, shy and excitable, and rather attractive in manner. Once their confidence has been gained they are very friendly. Their clean and tidy habits are remarkable. They avoid boisterous games and are punctual at school, usually keeping to the footpath on the way there and, to quote a schoolmaster, 'they are bright and intelligent and give their teachers little trouble.' They are always clean, even in a mining village. Relative to their social position their homes are above the average.

Their meals are regular and they are in bed at a reasonable hour. Invariably, one or both of the parents is of the nervous worrying type, and they devote much thought and energy to the proper care of their children and their homes, as did their parents before them. There is often a family history of similar attacks. The dramatic and recurrent nature of the attacks often creates an anxious parental atmosphere." This description is like a breath of fresh air in these days of laboratory medicine when the fundamental necessity of detailed and accurate clinical observation is insufficiently stressed in our teaching.

Dr King observed that these patients are nervous and easily disturbed in infancy, but are, at most times, contented babies. They are pale, thin babies, and teething is late, as a rule. He never observed an attack during the period of breast feeding. Urticaria was a common prodromal sign in babies and young children in his series ; it invariably receded before the commencement of vomiting. He described the course of an attack as follows : " The child is very fretful, pale, anorexic, and constipated. Sometimes there is diarrhoea. Eating causes nausea, and then the food is vomited a quarter to half an hour after 2 or 3 meals. This interval rapidly becomes shorter until the food is vomited immediately after ingestion, then vomiting occurs repeatedly, even when no food has been taken, and may persist for two to four days. Vomiting is less frequent during the night." I have observed that epigastric pain, which may be caused by the muscular strain of the act of vomiting, is a common feature when vomiting is persistent, also that headache is not uncommon and that prostration is the rule at the height of an attack. To continue King's description : " The breath smells strongly of acetone, commencing to do so in the prodromal stage. Then, without special treatment, and at any stage of the attack, spontaneous recovery begins, acetone disappears from the breath, and the child soon appears normal again. At the end of an attack the child is very pale, listless, and shows obvious loss of weight. The appetite and good health rapidly return, and lost weight is soon regained." King, in common with most other observers, did not find any regular periodicity of the attacks. The term " cyclic " is therefore misleading and should be discarded. A child may have a recurrence in weeks or months, or may not have another attack for years. Naso-pharyngeal infection is likely to precipitate an attack in a susceptible child and is probably the usual cause of the pyrexia which is a common feature. King emphasised that although no further attacks of vomiting may occur, acetone can often be found in the urine, especially when any of the premonitory symptoms or signs such as anorexia or urticaria occur. He observed that from the age of one to two years the nervous factor becomes increasingly noticeable, the attacks being associated with some form of excitement, and often with fatigue. Later the excitement associated with anticipation becomes an increasingly important precipitating factor, e.g. a Christmas Party. With the approach of puberty the incidence of attacks diminishes, and by the



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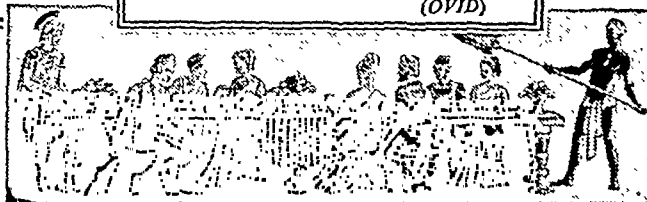
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time of puberty they have entirely ceased, but the patients remain shy and nervous. Dr King did not mention the occasional sequel of migraine in adult life; he never observed the condition in any of his patients, nor was there a history of it in any of their relatives, but his series of cases was small and he had not yet followed up many of his patients into adult life. Various other authorities have observed a significant relationship between recurrent acidosis in childhood and migraine in adult life.

The hereditary tendency to this disease is implied in the description I have given. King quoted one family in which the members, through four generations, showed typical physical and mental characteristics, and in which almost every child showed attacks of the disease at some stage of childhood. In another of his families there were five affected individuals in three generations.

King emphasised that in this disease acetonuria always precedes vomiting, whereas in vomiting from almost all other causes acetonuria succeeds vomiting. He also showed that the amount of acetone in the urine is a reliable indication of the likelihood of vomiting supervening. On estimating the amount of acetone as +, ++, or +++, he found that vomiting never occurred when it amounted to + and almost invariably did so when it amounted to +++.

The cause of the actual attacks of ketosis is still a matter of controversy. King, on weighing the experimental evidence in the literature and the clinical features of the disease, concluded that the excessive autonomic stimulation of the suprarenals, caused by the nervous excitement which induces attacks, produces an outpouring of adrenalin, and that the excessive amount of adrenalin reduces the glycogen reserve of the liver, thus creating conditions in which ketosis readily appears. This reasonable hypothesis accords with the transient nature of the attacks, the normal health between attacks, and the negative results of metabolic experiments in affected patients.

The main principles of treatment are physical and mental rest and a calm, confident atmosphere in the household. Since vomiting is less troublesome by night, and to ensure more complete rest, a darkened room by day may be helpful. Large doses of glucose and sodium bicarbonate, in water flavoured with fruit juice, should be given as often as possible, in sips, giving as much as can be retained. When the vomiting ceases half-strength skimmed milk with sugar should be introduced, and the diet is then gradually built up. Sodium bicarbonate should be continued until the urine is acetone free; this may not occur for three weeks or longer. Parents should be advised to give sodium bicarbonate and glucose whenever any premonitory signs of an attack appear. In a very severe attack, prolonged and persistent vomiting may lead to a severe enough degree of dehydration and metabolic breakdown to cause death. It may, therefore, be necessary to admit a child who has suffered much fluid loss to hospital for treatment with intravenous fluid, electrolytes and glucose, until, with improvement,

an adequate amount of fluid given by mouth can be retained. A sedative such as phenobarbitone in gr.  $\frac{1}{2}$  to 1 doses may help to allay excitement and apprehension. Phenobarbitone or morphia may be given parenterally if very persistent vomiting precludes the oral administration of a sedative.

### SOME OTHER FUNCTIONAL NERVOUS DISORDERS

I have discussed only a few functional nervous disorders of childhood. There are many others, some of which are frequently seen in general practice.

**NAIL BITING.**—This is a common nervous disorder which seldom occurs in a happy, confident child. It is a sign of emotional tension with an aggressive element. There is often an earlier history of thumb-sucking and it seems probable that such children, having discovered in the past that comfort could be found by employing the mouth, again resort to the mouth for relieving their tension. There is very often a family history of nail-biting, a sign of an unstable stock. Treatment consists of relieving the child's emotional tension, strengthening his self-confidence and feeling of security, and ignoring the nails.

**TICS (HABIT SPASMS).**—Tics are common in childhood and are usually associated with other signs of emotional disorder. Common types are shoulder shrugging, head jerking, blinking, grimacing and throat clearing. Tics must be carefully differentiated from chorea and fidgetiness caused by anxiety. One tic is not infrequently replaced by another. Tics may persist for long periods and are difficult to treat. Treatment consists of ignoring the tic completely, resolving the emotional difficulties which have caused it, avoiding fatigue, and improving the general health. A happier and fuller life with a feeling of security and self-esteem should be secured if possible.

**ENURESIS.**—Subnormal control of micturition more often has a psychological basis than a physical, especially when it occurs only at night, but organic causes such as urinary tract infection, thread-worms, diabetes, polydipsia, and, of course, mental defect, must always be eliminated with great care before a diagnosis of psychological enuresis is made. Psychological enuresis is usually only one of a group of emotionally determined symptoms and it is logical, therefore, to endeavour to discover and treat the common aetiological factors and to ignore the enuresis.

**ENCOPRESIS.**—Subnormal bowel control is much less common than enuresis, but it is more distressing. It is usually, in my experience, either a sign of severe psychological derangement or subnormal mental status. Here, also, organic causes such as chronic constipation must always be carefully excluded. Treatment is on the same lines as in psychogenic enuresis. It is usually desirable to invite the assistance of a child psychiatrist in these complex and difficult cases.

**FEARS, PHOBIAS, NIGHT TERRORS AND SOMNAMBULISM.**—These common conditions constitute a group of functional nervous disorders. They are common in children of school age up to the age of puberty, though their frequency diminishes after the age of ten years. Fear is the basic aetiological factor.

The fears of infancy are based on strangeness such as sudden loud noises and abrupt movements. As the infant grows older abnormal routine and environment are more important. After infancy fears take the form of being left alone, fear of the dark, and bodily injury—especially from animals. It is believed that fears at this stage of development are one manifestation of a real emotional disturbance, rather than a logical result of experience. Children who develop excessive fears have usually already formed neurotic patterns. There is often a history of disharmony with the mother over toilet training and feeding, while a lack of understanding of the child mind, with an insufficiently liberal attitude towards him, and parental disharmony, are often important aetiological factors. These children feel anxious and insecure.

Fears after the fourth and fifth years are increasingly illogical and mysterious and are usually known as phobias. At this stage of development the child concentrates all his fearfulness on one subject or situation and does not know why. Fear of an animal is the most typical phobia of a child of five years. The older child may, for instance, be afraid to go out of doors alone or be afraid to enter a room alone. A phobia is a protective mechanism which allows the patient to isolate and disguise his true fear.

Nightmares and night-terrors are fears operating during sleep when there is an inhibition of thought. The counteracting reassurance provided by reality during the day is lost in sleep, and the child's instincts and anxieties, which his phantasies arouse, run riot in the dream. The excitation becomes so great that it cannot be contained in the psychic sphere and encroaches on the physical sphere, causing the child to mutter, scream, and struggle, and perhaps sleep-walk.

Treatment of these disorders based on fear is essentially prophylactic with a view to reducing the child's anxieties to a minimum. Severe cases require skilful handling and should be seen by a child psychiatrist, whose object is to give the child confidence and enable him to bring his fears into consciousness where they can be understood and then dispelled.

**COMPULSION NEUROSIS.**—This common disorder most often occurs between seven and ten years of age. The child feels compelled to perform certain acts, such as marking time with feet or hands in a certain place, and to repeat them a given number of times, and although realising that they have no object and make him unhappy, there is a great urge to complete the self-allotted task. Such antics expose a child to ridicule and care is usually taken to avoid detection.

Like phobias, compulsions are a disguised repression of a deep



conflict. They are said to be a form of penance for having done something, or wishing to do something, the child imagines to be sinful, and which he has a strong impulse to do. Moreover, these "sinful" compulsions are of two principal kinds—sexual and cruel. The severe self-punishing mechanism of compulsions which makes a child do penance for sins he has not committed is a sign of the growing child's developing conscience and increasing repression of sexual instincts.

Treatment is protracted and difficult and should be undertaken by a child psychiatrist if possible.

OTHER DISORDERS.—Head banging, head rolling, religious mania, and most cases of stammering are other functional disorders which spring to mind.

### CONCLUSION

In conclusion I wish to reaffirm that a suitable soil, an unstable psychic heredity, usually forms the basis of functional nervous disorders in childhood, as in adult life. *Unfavourable environmental influences* are much more likely to cause these disorders in the children of an unstable stock, than in those with stable antecedents and a home with a cloudless sky, but favourable environmental circumstances are no guarantee against the development of these disorders in children hereditarily predisposed to them, since a considerable proportion of cases have such a background.

I have stressed the prophylactic aspect of treatment rather than the therapeutic. The management of established functional nervous disorders in childhood demands much time and patience, a sympathetic but firm attitude, and a breadth of outlook which can visualise the whole child, his inherited constitution, and the sum of all the environmental influences which make his world. In a word, treatment consists of the elimination of maladjustments from the child's life to the greatest possible extent. Undoubtedly, treatment of the mother, and of the child through the mother, are the principal objectives in the young patient, for the mother constitutes, and is responsible for, the major part of the child's environment in the early years. In the older child the mother usually remains the major influence, though the father, the school teacher and others, then play an increasingly important part. The history must always be exhaustive and include that of the other members of the family, school life, and all other relevant aspects of the child's life and relationships, and it should be supplemented from time to time as opportunity offers. Physical examination of the child should also be very thorough. It is important to realise that history taking and examination are essential parts of the treatment of patients with functional nervous disorders, for such care inspires confidence in parents and child and a desire to co-operate in treatment. After thorough investigation a therapeutic programme is envisaged. The nature of the child's illness and its probable causes are then

explained to the parents and, in the case of an older child, to the patient himself. Such explanation may do much to promote the necessary readjustments in the child's life. It is usually necessary to interview the mother and child at regular intervals of one to four weeks for a prolonged period extending over several months to a few years. Guidance can thus be given to the mother regarding the management of her child and opportunities are provided for gaining a greater understanding of the child's outlook and difficulties. Play therapy is often of great assistance in revealing the nature of a child's psychological problems and in treating them. Family doctors have the advantage of knowing the stocks from which their child patients come and they have the confidence and affection of their patients, but they lack the time which the investigation and treatment of these cases usually demands. In difficult cases, therefore, family doctors should enlist the help of a child psychiatrist. Child psychiatry (child guidance), which has developed slowly in this country, occupies, or should occupy, the leading place in the treatment of functional nervous disorders in childhood. Happily, this fact is now generally recognised and child guidance facilities, under the direction of experienced child psychiatrists, are now available in most large communities in this country. The child guidance clinic is the centre of a child guidance service and psychiatric social workers and a child psychologist are indispensable members of the team. Child psychiatrists should work in close liaison with pædiatricians to ensure a well-balanced approach to the whole child, since the physical and psychological components of an organism are inseparable and interdependent. It is desirable, therefore, for a child guidance clinic to be a unit of a pædiatric department, rather than to function in relative isolation and imbalance, as has too often been the case in the past.

I wish to acknowledge my indebtedness to Drs Benjamin Spock and Mabel Huschka and to Dr William S. Langford whose works have been of great assistance to me in the preparation of this lecture. I am particularly grateful to Dr H. M. King for permission to quote his Thesis on *Recurrent Vomiting with Acetonuria in Children*.

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## CHANGING CONCEPTS IN THERAPEUTICS

By D. M. DUNLOP, B.A., M.D., F.R.C.P.

THE post-graduates who have attended our course of instruction here during the last months have been kept pretty busy. Daily they have had to try to digest a great mass of factual information: the courses of the brachial plexus, the sources of organic fluids; the lesions of the spinal tract, the reasons for hæmoptysis; the drugs which bind the intestines, the bugs which turn them to water; and it would not be surprising if some post-graduates at the end of a term of this sort of thing were suffering from a little mental indigestion.

So you will perhaps forgive me if to-day my only object is to amuse and possibly to stimulate rather than to inflict more information on your heads, bloody, but I hope unbowed, with the bludgeonings of much learning. I do not, therefore, mean to speak to you about recent great concrete advances and discoveries in therapeutics—new drugs, new hormones, new physical methods—but rather about the changing attitude of mind in treatment—to contrast my own views as a middle-aged physician with what they were some fifteen years ago when I was a very young physician on subjects such as rest and exercise, dietetics and nutrition, cough mixtures, intestinal toxæmia, vaccines, allergy, psycho-somatic medicine and so forth.

### REST IN BED

"I'd put the patient to bed." All students invariably start their answer in this way to any therapeutic question set them. It does not matter whether they have been asked to treat typhoid fever or paralysis agitans, congestive heart failure or disseminated sclerosis, acute nephritis or mild diabetes—their opening gambit is always the same, "I'd put the patient to bed." They expect to get at least five marks for this sapient piece of advice, and that is what they would probably have got fifteen years ago, though to-day they often get five marks taken off, but it will take another decade to get them out of the habit, for undergraduates are creatures hoary with the tradition of the old masters. The dangers of going to bed have been reviewed in a spirited article by Asher. "Look at a patient lying in bed," he cries. "What a pathetic picture he makes—the blood clotting in his veins, the lime draining from his bones, the scybala stacking up in his colon, the flesh rotting from his seat, the urine leaking from his distended bladder and the spirit evaporating from his soul." Surgeons are realising the dangers of rest in bed more quickly than physicians—the risk of post-operative atelectasis, hypostatic pneumonia, thrombophlebitis and pulmonary infarction—particularly in middle-aged and elderly patients after an operation, and they are, as you know, getting them up earlier and earlier. It is curious that the nursing staff should

not constitute our most willing allies in keeping patients out of bed. Their work could be immensely lightened by a reduction in the number of bed baths, bed sores, bed pans and bed making, but they mostly prefer to immolate themselves upon the altar of tradition. It is not unusual, for instance, to see a miner, admitted to hospital for the investigation of some chronic complaint, who has been labouring at the coal face the day previously, and who has walked into hospital, being popped into bed by a traditional ward sister and shortly afterwards being perched upon a bed-pan. He must surely be dumbfounded by the whole affair and think us very singular people indeed.

Asher has sufficiently stressed the dangers of complete confinement to bed in respect of hypostatic pneumonia, atelectasis, thrombosis, infarction, bed sores, decalcification, renal stone, dyspepsia, constipation, disturbances of bladder function, wasting of muscle, foot drop, psychological demoralisation and deterioration in chronic nervous diseases such as disseminated sclerosis, tabes dorsalis and paralysis agitans, but it is worth while considering for a moment whether rest is not greatly over-prescribed even in many cases of acute rheumatic fever, coronary thrombosis and valvular disease of the heart. Fifteen years ago most clinicians advocated a minimum of three months' rest in bed even after a mild attack of acute rheumatic fever. We assumed the heart had been affected in every case till time had proved us wrong. For some years now I have had no hesitation in getting patients out of bed after an attack of acute rheumatism once the temperature and sleeping pulse and physical signs in the heart are normal, arthritic pain absent, and the sedimentation rate within normal limits for a fortnight—even though this may involve getting some patients out of bed within a very few weeks of the onset of their disorder. I have no reason to regret this practice, nor do I consider it necessary to keep *all* cases of coronary thrombosis in bed for as long as six weeks. Naturally convalescence after acute rheumatism should be protracted and carefully supervised, but may I here make a plea for more sense of responsibility to be shown in the diagnosis of rheumatic endocarditis. It is safe to say that for one young adult with a mitral stenosis that has been missed by his doctor one sees ten cases with innocent murmurs labelled organic. When such important matters are involved as the whole future life of a young patient, his choice of vocation or her fitness for eventual marriage and child-bearing, it is surely incumbent on the doctor not to be light-hearted in his diagnosis. As Mr Stanley Baldwin once rather surprisingly said, "Power without responsibility is the prerogative of the harlot throughout the ages."

Even when chronic valvular disease is well established the patient should be treated only when his symptoms warrant attention, and not his physical signs. There is no reason to suppose, when valvular incompetence is perfectly compensated, that the prescription of long periods of rest or of going slow will delay the onset of heart failure. It may indeed have the opposite effect. I had a patient who died

the other day at the age of 48 from a rheumatic aortic incompetence which had become manifest at the age of 16. In the intervening years he had become a notable mountaineer and had climbed the Matterhorn on three occasions. It is doubtful if he would have survived as long if some officious doctor had originally made a cardiac cripple of him as his alarming diastolic murmur and water hammer pulse might have warranted.

I do not, of course, suggest that rest in bed is not of immense therapeutic value in a great variety of conditions—all severe fevers, heart failure, acute nephritis, active rheumatoid arthritis, severe anæmia, tuberculosis, peptic ulceration and so forth—and especially for over-worked housewives if they are not too old, but I do suggest that complete rest in bed should be prescribed like a potentially dangerous drug, and not instituted as a matter of course for all hospital patients until the contrary has been ordered. Further, it should be exceptional rather than common for patients not to be allowed up to go to the lavatory.

#### NUTRITION AND DIETETICS

You can keep a pig in a hygienic porcelain sty, adjoining a green playing field in which it can disport itself, but it will be a pretty poor pig unless you feed it properly. Conversely, you can keep one in the filthiest sty and never allow it out, but it may none the less develop into a magnificent animal if it has plenty of good food. We are not very different to pigs in this respect. Good housing, adequate rest and exercise, and good food are far the most important factors in the maintenance of health—these three, but the greatest of these is food; and we have come to realise the importance of nutrition more and more in the last fifteen years. Just as, however, the importance of good nutrition in the maintenance of health has become more widely appreciated, so the prescription of complicated diet sheets for this and that disease has receded into the background.

Fifteen years ago I believed, along with many others, that a diet sheet had an almost mystical therapeutic potentiality. We had diets for hypertension, diets for rheumatism, diets for every stage of Bright's disease, ketogenic diets for urinary infection, step-ladder diets of alarming complexity for diabetes, diets for heart disease, Gerson diets for pulmonary tuberculosis, diets for asthma and of course a bewildering number of diets for various types of dyspepsia to which we usually gave names:—the Lenhartz diet; the Sippy diet and Hurst's modification of it; the Meulengracht diet and Witt's modification of it; Schmidt's intestinal diet; the pulped apple diet; Sprigg's lacto-vegetarian diet and many others. We were apt to look upon these diets as entities in themselves, prescribing them rigidly to the bank clerk, the night watchman, the stockbroker and the miner. Simple scientific principles were often lost sight of and fashion and tradition made endless impositions but particularly restrictions which

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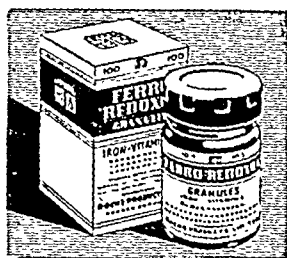
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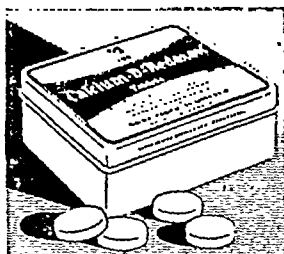
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were very often unjustifiable on any rational basis. Our diets were almost always inconvenient to the patient and often actually detrimental to him from the point of view of sound nutrition. Consider the monotonous white flaccidity of the sloppy Sippy diet, practically foreign to iron and apart from its mashed potato, to vitamin C. Generations of dyspeptic women must have become more anæmic upon it, and I have known a conscientious young man, who did not like potatoes, stick to it in other respects so rigorously that he was rewarded for his efforts by developing frank scurvy. Apart from the fact that patients on a Sippy diet fed frequently it is doubtful if the regime did any good at all. Frequent small meals of ordinary well-mixed foodstuffs remain far longer in the stomach and thus have a far better neutralising effect than the pappy-feeds ordered by Sippy, which pass out of the stomach with remarkable speed.

Consider also the post-operative diets imposed by most surgeons fifteen years ago on patients who had had a gastro-enterostomy or other operation on the stomach. Nothing but a few sips of sterile water was given for the first two days (why sterile it is hard to imagine) and thereafter the diet was built up by painfully slow and exiguous additions, so that it took at least a fortnight before the patient was being at all adequately nourished. Quite apart from the suffering imposed by starvation, this old-fashioned post-operative regime must have seriously retarded the recovery of many and killed not a few by exaggerating the catabolic phase and negative nitrogen balance inseparable from major surgical procedures. We now realise that unless a surgeon can make his anastomosis milk-proof and water-proof a patient will not live to take a diet at all, but if the surgeon is successful in this respect there is no reason why the patient should not be taking an adequate diet within a very few days of operation. Further, we have come to appreciate the paramount importance of pre-operative measures to ensure adequate nutrition in preparation for the post-operative catabolic phase. I remember as a house surgeon the hideous eighteenth century purgations and starvation which we inflicted on our patients in preparation for abdominal surgery, and how surprised we used to be that emergency cases, who had not had the benefit of our eliminative ministrations, progressed so well after operation.

The difference in our attitude to medical dietetics between now and fifteen years ago is the difference between the new and old testaments—Thou shalt, rather than thou shalt not. We are much more interested in seeing that the patient eats a sufficiency than in forbidding him this or that article of diet. "Avoid butcher meat" was the cry of the older physician to the chronic nephritic, the hypertensive and the dyspeptic; now there is hardly a single chronic disorder in which we do not encourage our patients to eat their full ration of meat or indeed in which we are not tempted to sign certificates for a more generous supply. Confronted with a patient who had just had a hæmatemesis, the physicians of fifteen years ago said,



"Don't give him anything to eat at all," and they even mocked him in his agony of thirst by giving him 6 oz. of saline per rectum, so that he, wiser than they, was driven to surreptitious drinks from his flower vases and hot-water bottles. Now, Meulengracht advocates stuffing down minced meat and green vegetables when the blood from a recent hæmatemesis is still drying on the patient's lips—a ludicrously exaggerated, if salutary, *volte face*—for patients who have just been very sick do not want minced meat and pureed vegetables, but rather a simple fluid regime for a day or two, which it is surely unnecessary solemnly to designate as, "Witt's modification of Meulengracht's diet." "Avoid fats," advised the ancients to the jaundiced sufferer from hepatitis. "Take plenty of glucose and a sufficiency of sulphur containing amino-acids," rejoin the moderns. On the whole a good cook is much more important in the management of sick people than a diet sheet.

To what extent are dietetic restrictions still justifiable? A detailed restrictive sub-caloric diet sheet is necessary in the treatment of obesity, and is one of the most valuable therapeutic measures in medicine, too often forgotten by physicians and surgeons in their management of flat foot, varicose veins, ventral hernia, osteo-arthritis of the knees and hips, gallstones, diabetes, heart disease, hypertension and bronchitis; fat should be rigorously restricted in the steatorrhœas, other high residue foodstuffs in chronic diarrhœa, and salt in the œdema of cardiac failure and the nephrotic syndrome, and possibly also in hypertension. Otherwise there can be few indications for restriction in medical dietetics. Even in diabetes there is an increasing body of opinion that, if the patient is not overweight, carbohydrate and calories need not be greatly restricted provided their intake is relatively constant from day to day so as to match the dosage of insulin. The protagonists of this view claim that if insulin is required at all it does not very much matter to the patient whether the dose is 30 or 40 units a day, whereas it does matter to him very much that he should be able to take a normal sort of diet. Lastly, modern research suggests that gout is entirely an abnormality of endogenous purine metabolism and that exogenous purines in the diet have no influence upon it at all. I confess to being an old-fashioned clinical impressionist in this respect and from my experience of certain patients with Chancellor's gout I find it very hard to swallow the theory that had young William Pitt not been in love with vintage port he would have suffered from the gout to the extent which he did.

#### POLYPHARMACY

It is of course platitudinous to say that with the advent of potent new drugs the polypharmacy of the early part of the century has practically vanished among modern physicians who attempt to practise rational medicine. There are still those who say, however, "But the public demand a good bottle and after all it has a great psychological

effect"; but the public demand to have their spines manipulated by osteopaths and chiropractors and after all *that* has a great psychological effect; what we condemn in others we should not condone in ourselves. We should rather attempt to educate the public in rational methods of therapy, even though the desire to take medicine is the chief thing which differentiates man from the lower animals.

It may, indeed, be doubted whether it is almost ever necessary to prescribe more than one drug in a bottle, pill or powder, apart from the vehicle and flavouring agent. True synergy, demanding the giving of two medicines together in this way, is very rare in pharmacology, though the combination of codein and acetyl salicylic acid might be exempted from this generalisation.

### EXPECTORANT COUGH MIXTURES

Fifteen years ago the revolt from polypharmacy was of course in full swing, though not so pronounced as it is now. A curious exception was the expectorant cough mixture, in which most people then still believed, though many doubt its value now. There has never been any scientific proof that expectorants in the doses employed are of any value at all, and I find it quite impossible to believe in the fantastic theory that tiny doses of ammonium carbonate, tincture of ipecacuanha and ammonium chloride will reflexly produce a mild degree of the salivation and associated bronchorrhœa which you see occurring in fellow passengers on a Channel passage when they start to swallow ominously. Ammonium chloride is usually prescribed in cough mixtures in doses of 3 to 5 grains, whereas we give doses of 30 grains to make the urine acid, and yet patients who take such large doses do not spend their time coughing up quantities of thin liquid sputum.

Potassium iodide is often added to such mixtures and it still has its advocates as an expectorant. It is undoubtedly excreted by the bronchial, salivary, nasal and lachrymal glands, and may occasionally in susceptible persons cause greatly increased secretion. When patients suffer from iodism they run at the eyes, nose, mouth and no doubt at the bronchi as well. There is no reason to believe, however, that they will run at their bronchi without running at their eyes and nose, and short of iodism it is very doubtful whether potassium iodide has any expectorant effect. Many doctors apparently believe that potassium iodide will have its action on just those glands which they wish it to affect without influencing other glands at the same time. The same touching belief is shown in atropine or belladonna which are often expected to relax spasm without making the patient the least uncomfortable in respect of dilated pupils and a dry mouth.

### INTESTINAL TOXÆMIA

Fifteen years ago the influence of Arbuthnot Lane was still heavy upon us. In his latter years the great surgeon had not stuck to his last and had wandered into more recondite fields where he had

discovered the colon as the nigger in the wood pile of health. I hope you will pardon my mixed metaphors. In Edinburgh we had our own enthusiastic and very eloquent advocate of intestinal toxæmia as the cause of all ills. Perhaps it was appropriate that in a city where James Gregory had flourished the cult of purgatives and colonic lavage should have had a fierce Indian summer. No one will deny that it is still having a productive autumn when we consider the vast sums of money still spent by rich and poor alike on purgative medicines.

Nowadays most of us are becoming increasingly sceptical of the part played by intestinal toxæmia in causing ill health and believe that moderate constipation is deleterious more from its psychological than from its organic repercussions, and that it is indeed very preferable to the over-enthusiastic daily use of purgatives. We believe further that dyschezia or failure of the rectal reflex, frequently brought on by the catching of the 8.30 in the morning, is a more potent ætiological factor in constipation than atony of the bowel produced by a low residue diet, and that this rectal reflex can almost always be recaptured by those who seek earnestly enough after it no matter whether it has been lost long since or only for a while ; we believe that colonic lavage as a routine, apart from an emergency measure, should not be practised, and that the injection of autogenous vaccines made from the *faeces* serves no useful purpose.

### VACCINES

It is interesting to consider how vaccine therapy has fallen into desuetude. Fifteen years ago all manner of disorders were treated in this way. Now vaccines are known to be of value prophylactically only in rabies, typhus, typhoid, smallpox, plague, cholera and whooping-cough and very likely the B.C.G. vaccine may have a future in tuberculosis ; but it is highly doubtful if vaccines are of proved value in the *treatment* of any established disease.

### ALLERGY

Fifteen years ago I was an enthusiastic hunter for allergens responsible for asthma, and remember the unprofitable hours which I spent skin-testing my patients—particularly the old asthmatic wife from the Cowgate whose skin test was positive to one thing and one thing only and that was to caviare ! I remember too the asthmatic Edinburgh business man who had only two nights each month of freedom from his affliction and those were the nights on which he journeyed up to and down from London for his monthly meeting. In his sleeper he slept like a child. It occurred to me that the pillows in sleeping cars were stuffed with some composite material and not with feathers, and that he might be allergic to feathers as his skin test strongly suggested ; and so every pillow and cushion in his house was ripped open, the feathers removed and the composite material installed (it was possible to do that sort of thing in those days), but

the asthma was as bad as ever. I had not realised that there was that in his nuptial couch but not in his sleeping berth to which he was far more allergic than to feathers. Why is it that asthmatic children, no matter how bad they are at home, practically never have an attack of asthma in hospital? Is it that the hospital dust and hospital food are so allergen free in comparison to the dust and food at home, or is it that they are allergic to their parents who project their own fears into the childish mind—to the father whose first question as he hangs up his hat on coming home is, "How has Maggie's chest been to-day," to the mother who tiptoes into the child's bedroom at night to listen with such anxious solicitude for the laboured breathing of the little sufferer? No one doubts the allergic factor in many cases of asthma, but we are increasingly sceptical of the paramount value of skin testing and of the methods so often used in desensitisation both in asthma and in hayfever. Desensitisation to a known allergen is a skilled, laborious business, not free from risk and frequently unsuccessful. Apart from intensive methods which must be carried out by a specialist in hospital, desensitisation involves the patient and doctor in almost daily interviews for weeks or months. The facile method of giving a few injections, say, of a mixed pollen vaccine a week or so before the hayfever season is to my mind a mere concession to psyche rather than a serious tribute to soma. Fortunately the discovery of anti-histamine drugs has provided us with a more hopeful approach to the treatment of superficial allergies such as urticaria, angioneurotic oedema, hayfever and paroxysmal rhinorrhœa, though these drugs are curiously ineffective in dealing with the deeper and more complex visceral allergies such as asthma.

### PSYCHO-SOMATIC MEDICINE

We realise much more than we used to do even fifteen years ago the psychological basis of many of the functional disorders which we treat. Just as the acute emotions produce their physical analogues by way of autonomic or hormonal influences, causing the tachycardia of excitement, the nausea of disgust, the diarrhœa of fear and the blush of shame, so more complex stresses and strains may be responsible for migraine, bronchial spasm, dyspepsia, spastic colon, amenorrhœa, urinary frequency, etc.—nay more, even for organic change such as peptic ulcer and ulcerative colitis, as the work of Wolf and Wolff on their modern Alexis St Martin has suggested, or for a whole host of organic disorders if we are to believe the brilliant and provocative theory propounded by Seelye in his alarm reaction. This more thorough realisation of the effect of psyche on soma is bound to have a profound and salutary effect on our management of patients—just as the teaching of Freud, even though we may not agree with, or may never have read his works, has had a profound effect on the behaviour of people to one another, to children and to criminals.

It should make us consider the patient as a whole man with a background, rather than as a lung, a heart or a stomach. I was examining the other day in Birmingham, where the final year students had for the first time had the advantage of an intensive course in social medicine. In presenting their long medical cases to me they invariably dealt with such questions as family income, housing, type of employment, diet, etc. Their enquiries about outside closets, marital relationships and so forth, often crude, ludicrous and inapposite, had sometimes black affronted their patients and caused the Professor of Medicine, who was an enthusiast for the scheme, to have to put up with a lot of derisive humour from his colleagues—but this attempt, which is now widespread, in the medical curriculum, to relate the background of a man to his illness and its management is one of the most hopeful advances in medicine to-day. You may say "But good physicians have always done this." I agree, and sometimes they have tried to teach it, but on the whole its importance up till now has never been stressed sufficiently in the teaching of clinical medicine, which is still dominated by the cases used in the final examinations—aneurysms pulsating through the sternum, Charcot joints, gross endocarditis, spleens in the right iliac fossa and pulmonary cavities sighing out their amphoric breathing to the accompaniment of consonating crepitations—good teaching cases, that is cases which will hardly ever be seen by the student again.

It is true that the mere appreciation that asthma and other functional conditions may be due to psychological stresses and strains may not help us much in their treatment. As physicians rather than trained psychologists we may not elucidate the factors which are involved, while the intensive treatment of the few by psychologists must always lack universality of application. Further, as physicians we are often unable to alter the environmental background of our patients. Still if we are sensitive physicians; if we are kind; if we are physicians who are men of the world we can do a great deal by ordinary encouraging suggestion and by wise advice, especially to the simple people who form the majority of our patients.

If we are in a better position than our fathers to appreciate and to correct the factors which produce illness there is yet the grave danger that whole-time hospital physicians brought up in the rarefied and precious atmosphere of the laboratory and who have never been in active practice, and students trained by medical professors who are sometimes clinical scientists rather than doctors, may lack the attributes of the old-fashioned doctor at whom I have poked a little fun in this lecture, but who has warmed both his kindly hands before the fire of life. I am sometimes a little alarmed that in scientific highly specialised units the patient as a whole man—a sensitive man—may be a forgotten. So often no one takes the trouble or has the time to tell him in simple terms what is the matter with him and what people are trying to do for him, which gives so much comfort and is

therefore such an important therapeutic factor. There he is allowed to lie, frightened, mystified, worried, while his case is discussed in entirely impersonal terms, as though he was really an internal combustion engine with a leaking valve. I have known women of the hospital class, for instance, who have allowed themselves to be practically eviscerated by some surgeon, without the slightest idea what organs have been removed or the reasons for their removal. There is no need to convert our patients into the type more commonly found perhaps in America, who prate ad nauseam of their blood ureas, B.M.R.'s and cardiograms; but there is a happy medium, and in this country I think we err on the side of the Balaclava attitude, "Their's not to reason why, their's but to do and die." The truth of it is that, as in other things, the greatest therapeutic gift is Charity and that is not a changing but a permanent concept in therapeutics.

## THE DISCOVERERS OF THE THORACIC CARDIAC NERVES

By G. A. G. MITCHELL, Manchester University

BECAUSE of their importance in connection with the surgical treatment of angina pectoris the thoracic cardiac nerves are small objects of great interest. It is therefore surprising that amongst the many articles and books dealing with the subject of cardiac innervation which have appeared since these nerves were first described, not one provides accurate information about their discovery. Judging from some of these writings, their very existence is not universally recognised, so it may be advisable to explain briefly that the cardiac plexus, amongst many other branches, receives slender contributions from the second, third, fourth and possibly fifth thoracic sympathetic ganglia and that these constitute the thoracic cardiac nerves.

Apart from the works mentioned later, no details of the thoracic cardiac nerves have been found in any of the great anatomical monographs, atlases and textbooks published during the nineteenth century. Early this century Mollard (1908) produced an elaborate monograph on the cardiac nerves, but he described none arising from the sympathetic trunks below the level of the first thoracic ganglia, although he quoted from the works of such men as E. H. Weber (1815) and G. Valentin (1843) who had found cardiac branches arising at a lower level. Those writing exhaustive monographs seldom succeed in assimilating completely all the information contained in the works listed in their impressive bibliographies, and Mollard was no exception. J. Dogiel, either alone or in collaboration with others, published many papers on the heart over a period of about thirty years, but he too remained unaware of the existence of the thoracic cardiac nerves. Perman (1924) and Müller (1924) both wrote at length about cardiac innervation and the former described thoracic cardiac nerves in the calf. Dresbach and Waddell (1926) detected connections between the cardiac plexus and the thoracic sympathetic trunks as far down as the fifth ganglia; Kondratjew (1926) found these nerves in man; and Cannon, Lewis and Britton (1926) realised from their experiments in cats that complete elimination of cardiac accelerator fibres required extirpation of the sympathetic ganglia as low as the sixth or seventh thoracic segments. Woollard (1926) published another long article about cardiac innervation in the same year, but admitted that he had relied on writers such as Mollard, Perman and Müller for his survey of the earlier literature.

In 1927 and 1928 two excellent articles appeared containing descriptions, amongst other things, of the thoracic cardiac nerves in man. They were written by Braeucker (1927) and by Ionescu and



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corresponding filaments in man, but he did not indicate anywhere that thoracic cardiac nerves exist in man similar to those in the calf.

Joseph Swan's atlas, published in 1830, was based on dissections which gained two collegial anatomical prizes of the Royal College of Surgeons in 1825 and 1828, and in most respects its plates of the nerves, and particularly those of the autonomic nervous system, surpass in detail and accuracy those decorating modern textbooks. He depicted and described right and left thoracic plexuses, formed by branches from the inferior cervical and upper four thoracic ganglia, which contributed to both cardiac and pulmonary plexuses. This is the earliest reference one has traced to cardiac contributions in man arising below the level of the first thoracic ganglion. The thoracic plexus of Swan should not be confused with the *ramus splanchnicus supremus* of Wrisberg (1800), reputedly formed at the root of the neck by contributions from the cervical cardiac, recurrent laryngeal and main vagal nerves. He said that this ramus, after a variable downwards course within the thorax, occasionally joined the posterior vagal trunk or entered the abdomen alongside the aorta to end in the coeliac plexus; along its course it might receive filaments from the thoracic sympathetic trunk and distribute offshoots to the aorta, thoracic duct, pericardium, lungs and oesophagus. The existence of Wrisberg's complicated highest splanchnic nerve is by no means certain, but it is certain that some of the filaments he described do exist, although they are not arranged quite in the way he imagined. It is probable he observed the filaments now described as the thoracic cardiac nerves in part of their course, but failed to trace them into the cardiac plexus.

It is imprudent in investigations of this type to state with absolute certainty who first described any particular anatomical fact, because no worker has access to, or the time to read, everything written on the subject. With this reservation, one believes that Ernest H. Weber and Joseph Swan deserve the credit for discovering the thoracic cardiac nerves in the calf and man respectively, at least one hundred years earlier than is usually stated.

My thanks are due to Professor W. Schlapp and Mr F. C. Hirst for providing certain exact translations from German articles.

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## POINTS OF LOCAL CHEST TENDERNESS IN POST-OPERATIVE PULMONARY EMBOLISM

By C. KELMAN ROBERTSON, M.D., D.P.H., F.R.C.P.

Assistant Physician, Royal Infirmary, Edinburgh

ANY clinical sign that can help in the early recognition of a post-operative pulmonary embolus must be considered of value in view of the desirability of instituting anticoagulant therapy as soon as possible.

A large rider embolus which straddles the bifurcation of the pulmonary artery some days after operation is such a dramatic event that the physician or surgeon is rarely in doubt as to the cause of the patient's collapse. The appearance of a medium-sized clot is usually made manifest by well-recognised clinical signs plus other features such as an ominous "little kick" of temperature, cough, pleuritic pain, and maybe the expectoration of blood-stained sputum. A small clot, however, may cause no obvious pulmonary embarrassment, but if recognised at once can act as an aura of later possible embolus formation which may end as a major catastrophe unless appropriately treated.

In the beginning the difficulty with the diagnosis of small pulmonary emboli is very real because few, if any, of the classical signs and symptoms may be present. There will probably be no rise of temperature, no obvious inspiratory pleuritic pain, no cough, and no streaking of sputum with blood for two or three days. Likewise at this stage X-ray examination cannot be relied upon as it is recognised that parenchymal density following a pulmonary blood clot may be absent or minimal for some days.<sup>1</sup>

Although attention is always focused on the lower limbs of a patient who has just been operated upon, clinical evidence of phlebitis is not always forthcoming, as the venous thrombosis arises in about 50 per cent. of cases above the level of the superficial femoral vein.<sup>2</sup>

It has been found, however, that an added chest sign, which has already been noted in the literature, can sometimes be of value in the early recognition of small post-operative pulmonary emboli, but as only two articles,<sup>3, 4</sup> dealing with this aspect of the subject can be traced it seemed justifiable to place on record corroborative findings in similar cases.

A definite point of local tenderness on slight pressure of the chest wall in relation to the area of infarction has been found in the following post-operative cases and brief clinical notes of each appended.

CASE I. Female, aet 27.—Operation: Gilliam with partial resection of right ovary.

Four days after operation pain developed in the left side of chest. Lungs clear and no pleuritic friction. Local point of tenderness to digital pressure in the 6th intercostal space on the anterior axillary line. The following day

temperature 100°, pleuritic pain and friction, cough. No Homan's sign. Next day blood-stained sputum.

Recovery : satisfactory one week.

CASE 2. Male, aet 77.—Operation : trans-urethral diathermy resection for fibrous prostate.

Six days after operation pain left side of chest and annoying cough. Temperature raised. Slight percussion dullness left base. No pleuritic friction. Homan's sign positive left leg. Local point of pressure tenderness 8th interspace posterior axillary line.

Recovery : satisfactory ten days.

CASE 3. Female, aet 26.—Operation : pelvic floor repair and sterilisation.

Ten days after operation temperature 101°. Cough, purulent sputum. Generalised bronchitis, no other pleuro-pulmonary localising sign. Dull pain left side chest. Local point of surface tenderness 7th interspace post axillary line. No Homan's sign. Staining of sputum two days after temperature rise. X-ray. Generalised increase broncho-vascular markings and emphysema.

Recovery complete. No point tenderness forty-eight hours after rise of temperature.

CASE 4. Male, aet 77.—Operation : excision papillomatous tumours of bladder with diathermy.

Six days after operation slight temperature with pain over left base. Cough unproductive. Homan's sign negative. Clinical examination of the chest negative. Acute local point tenderness 6th interspace anterior axillary line. On the following day a pleural friction rub was audible over the affected area and sputum was bloodstained.

Recovery : satisfactory in ten days.

CASE 5. Female, aet 61.—Operation : pelvic floor repair.

Nine days after operation pain left side of chest, temperature 100·8°, dyspnoea. Slight percussion impairment left base. Acute local point tenderness 7th interspace posterior axillary line. Positive Homan's sign left leg. Heparin anticoagulant therapy and penicillin given. Definite leg phlebitis on twelfth post-operative day. Recurrent small left basal emboli.

Recovery : one month.

CASE 6. Male, aet 55.—Operation : prostatectomy.

Pleuritic pain left base six days after operation. Negative Homan's sign. Audible friction rub left axillary zone. Local point tenderness 6th interspace midaxillary line. On the following day sputum was bloodstained, temperature 100°. X-ray negative.

Satisfactory recovery in one week.

Sudden recurrence of chest pain with physical collapse seven days later, clinically consolidation left lower lobe. X-ray parenchymal density lower lobe left lung.

Recovery : three weeks.

CASE 7. Female, aet 35.—Operation : Cæsarean.

Five days after operation pain lower left side of chest. No temperature increase. Negative chest findings. Local point of tenderness 6th interspace

anterior axillary line. Two days later staining of sputum and signs of consolidation left base. Homan's sign positive one week after onset of chest pain.

Recovery : satisfactory.

CASE 8. Female, aet 41.—Operation : hysterectomy.

Slow post-operative convalescence. Eighteen days after operation acute pain right chest with sudden physical collapse. Oxygen and cardio-respiratory stimulants given. Local point tenderness 7th interspace posterior axillary line. On the following day there was rise of temperature with blood-stained sputum. Homan's sign positive followed by obvious phlebitis in left leg two days later.

Recovery : complete.

Although this sign of local thoracic tenderness is recorded as an additional guide to the early diagnosis of pulmonary infarction, it is not always present, as it has only been possible to elicit it in 8 out of 53 post-operative cases examined during the past five years.

The point of tenderness, if present, is always truly localised and defined and in two of the cases (4 and 5) was really exquisite as a moderate degree of finger-tip pressure caused the patients to cry out with the intensity of the pain. The true relationship between the appearance of this pain and other recognised signs and symptoms associated with infarction, cough, pleuritic pain, etc., would indicate that the upset, at the time it is found, lies not in the lung but in the intercostal tissues.

The lungs and visceral pleura are insensitive of pain. The parietal pleura, however, is particularly sensitive, and it has been considered that pain sites are mostly concentrated over its lateral and ventral aspects. Local surface point tenderness could be due to irritation of the underlying parietal pleura, but this cannot be the sole cause as in some of the cases the degree of pressure exerted was insufficient to compress anything but superficial tissues. This would infer that the pain is probably muscular. Muscle spasm is a well-recognised cause of chest pain and no doubt this is the responsible factor in relation to local surface tenderness in cases of post-operative pulmonary infarction. The spasm being the result of an impulse transmitted from the pleura to the cord, and then via the corresponding motor nerve to muscle and sensory nerve.

Chest pain arising in a patient who has recently been operated on makes us consider the possibility of a pulmonary embolus, but it may be that few, if any, other associated clinical findings are present, and it is therefore recommended that local point tenderness be searched for as it can help in the early diagnosis of this condition.

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## OBITUARY

### ROBERT CRANSTON LOW

ROBERT CRANSTON LOW was born in Edinburgh in 1879 and died on 3rd February 1949. He received his early education at Merchiston Castle School, and graduated in medicine with honours at the University of Edinburgh in 1900.

Allan Jamieson, then at his zenith as a clinical teacher, introduced Low to dermatology and so stimulated his interest in the subject that he decided to specialise in it. After completing several terms as a house physician in the Royal Infirmary and the Royal Hospital for Sick Children, he proceeded to Neisser's clinic in Breslau, and later to Unna in Hamburg, in all spending some two years on the continent in the study of dermatology.

His sojourn in Breslau coincided with important advances in bacteriology, some of which were made by Neisser and his co-workers, and with the development of the modern concept of immunology. This period left a permanent impression on a mind naturally alert and quick to respond to new ideas, and throughout his medical career Low regarded his specialty from the critical viewpoint of the experimental worker. On his return to Edinburgh he commenced the study of the newly recognised phenomenon of anaphylaxis; the results of his own experiments and a masterly review of the whole field formed the subject of a thesis presented in 1924 for the M.D. degree, for which he was awarded a gold medal, and which was later published as a monograph. His main contribution to the problem was the experimental production of cutaneous sensitivity to *Primula Obconica* in the human, and he was the first to make this observation. It was a discovery which marked an important advance in the understanding of idiosyncrasy, and it established a principle on which is based much of the present-day conception of eczema and allied skin diseases.

Low was appointed Assistant Physician to Sir Norman Walker's wards in the Skin Department of the Edinburgh Royal Infirmary in 1906 and full Physician in 1924. He retired from active charge of the department in 1933, and continued his association with it in a consultant capacity. During this time, in addition to conducting a large private practice, he was much occupied in the teaching of dermatology to undergraduates and postgraduates, a task which he carried out in a most stimulating manner. His *Diseases of the Skin*, a handbook for students and general practitioners, was published in 1927, and is now in its third edition.

He was responsible for the gradual collection of the large number of moulages which the University is now fortunate in possessing. While studying in Paris he himself learnt the technique of cast-making from Baretta, not without some opposition as he used to recount with relish, for the secret of the ingredients and the process was at that time somewhat jealously guarded. He introduced the method at Edinburgh, and his artistic ability lent itself to this work, casts made by him being amongst the most perfect in the collection. This leaning towards the fine arts was again in evidence at a later date, when during a short period following his retirement from medical work he devoted his energies to painting.

This period of separation from medicine was short-lived, however, for notwithstanding a multiplicity of outside interests, Low found soon after his retirement that his interest in medicine could not be easily discarded. His early enthusiasm for the laboratory returned, and in the Bacteriology Department of the University he commenced an investigation on the pathogenic fungi. At the outbreak of war a shortage of staff in this department led to his once more undertaking teaching duties, which he continued until 1945. At this time the dermatologist had become a bacteriologist, and the result of the transformation was the publication of an *Atlas of Bacteriology* which was everywhere acclaimed with enthusiasm. For the last three years of his life he acted as Curator of the College of Physicians' Laboratory and in this short space of time his influence was apparent.

Cranston Low was a distinguished figure in British Dermatology, and his contributions to it were valuable. By personal contact with his colleagues, who held him in the highest esteem, he did much to stimulate progressive thought. Throughout a span of nearly fifty years his devotion to medicine and to its advancement was unswerving.

## NEW BOOKS

*Fundamentals of Neurology.* By ERNEST GARDNER, M.D. Pp. xi+336, with 134 illustrations. London: W. B. Saunders Co. Ltd. 1947. Price 24s. net.

This book has several unusual and attractive features, notably the valuable way in which the author deals with the history of neurology and describes the way in which workers' names have come to be associated with different developments throughout the years. This aspect will intrigue students and often others who may be surprised at their ignorance.

The functions and structure of the nervous system are carefully presented in such a way as to create a well-founded basis for the later approach to clinical work, a description of which is no part of the author's purpose. The text is much helped by the different diagrams and photographs, a few of which are old favourites, but many new and well thought out.

Physiological rather than anatomical is the approach to neurology that is stressed, wisely no doubt in a work which must be regarded by clinicians particularly as providing information solely complementary to their daily requirement. Yet saying this is not to deny the essential quality of the book.

*Psychiatry.* By WILLIAM A. O'CONNOR, L.M.S.S.A., D.P.M. Pp. 392. Bristol: John Wright & Sons Ltd. 1948. Price 35s. net.

This book is, like every short treatise, too dogmatic and arbitrary. The author is unnecessarily severe on those who may not hold the same views as he himself does. For the most part the clinical descriptions are adequate, but the forensic aspects of psychiatry are not considered at all. It could not be recommended as an adequate guide or help to students.

*Tuberculosis.* By FRANCIS MARION POTTENGER. Pp. 597, with 104 illustrations, graphs, etc. London: Henry Kimpton. 1948. Price 60s. net.

There are books and to spare on tuberculosis but the writings of an individualist command attention. This work covers the general field of tuberculous infection and disease and there is a good chapter on the disease in childhood. To that extent it perhaps reproduces in a degree what other books contain. This book, however, is founded on the long clinical experience of one man, and views based on that experience are expressed in a forthright way. Although he gives full place to the ancillary methods of diagnosis and disease control Dr Pottenger writes as a clinician and it is refreshing to read the writings of one who believes that hands, ears, eyes, and judgment still count in medicine. The author is perhaps best known for his work and views on what he calls the visceral neurology of pulmonary tuberculosis and if we cannot follow all of his views in this field, or feel that our senses possibly lag behind his, we can at least derive a stimulus from his enthusiasm and sincerity. We can also renew our faith in the clinical approach to our work. The book is a useful and welcome addition to the literature of tuberculosis.

*The Nature of Disease Institute.* By J. E. R. McDONAGH, F.R.C.S. Pp. xiii+174. London: William Heinemann (Medical Books) Ltd. 1948. Price 21s. net.

The Picasso of modern science has produced yet another masterpiece proving that all diseases are one disease caused by an abnormality of the plasma proteins. The structure of the protein molecule (frontispiece) corresponds roughly to the "Lady with the Fish Hat," but is even surpassed by the formula for nucleic acid (p. 67) which has acquired atoms of iron, potassium, calcium, sulphur and chlorine never put there by Nature.



According to the author, the protein molecule is an animated concertina, expansion or contraction of which gives rise to all known diseases, and which plays all tunes from the allegro of smallpox to the andante of testicular tumours. And it frequently plays a discord. The chemist may be pained to read of nitrogenous hydrocarbons and the chlorine atom of acetyl-choline (p. 59); the therapist surprised by the fact that insulin has always given excellent results in Paget's Disease (p. 30); the pathologist horrified by the statement that "Diabetes mellitus is an inherited manifestation of disease caused by over-contraction of the middle third of the radiator-functioning portion of the protein" (p. 41); but the student will be comforted by the fact that there is now only one disease to study; and the licentious will rejoice that the *spirochæta pallida* is no longer the cause of syphilis (p. 15).

The last section of the book is devoted to sixteen selected case histories ranging from senility to auditory nerve tumour. Each case is described with occasional references to treatment, and the reviewer can only marvel at the sagacity which has prompted the author to draw a discreet veil of obscurity over the progress and ultimate fate of each and every patient. That the author confesses (p. 119) to have hawked his concertina around the Continent without meeting a prospective buyer will cause concern, but not surprise. More ominous is the caption "First Annual Report" which forebodes a grim threat of further desecrations of the country's already impoverished supply of newsprint.

*Constitutional Medicine, Endocrinology and Allergy.* Edited by E. PULAY, M.D., and P. LANSEL, M.D. Volume II, 102 pages; volume III, 64 pages; volume IV, 114 pages. London: Frederick Muller. 1948. Price 10s. 6d. net per volume.

The aim of these publications is to offer physicians all the advances in clinical medicine considered from the viewpoint of constitutional medicine, a term which is taken to mean the psycho-physical structure of the individual.

Each volume contains about half-a-dozen articles on the most diverse subjects written by British and foreign authors. "Allergy and liver," "Speech and voice disorders in Puberty," "Intrinsic factors of tumour formation," and "Polymorphous erythemas," will give some idea of the range of subjects covered.

*Medical Research in War.* Pp. 455. London: His Majesty's Stationery Office. 1948. Price 7s. 6d. net.

This compilation issued under the auspices of the Medical Research Council describes activities during the period 1939-45.

It gives a great deal of information about important investigations in many fields of medical work and might be considered as a review of British Research in recent years. The most outstanding article is an account of the development of penicillin but there are many other subjects of absorbing interest. Each section gives lists of papers published under the Medical Research Council.

A very creditable record of work done.

*Diseases of the Breast.* By Sir CRISP ENGLISH, K.C.M.G., F.R.C.S. Pp. vii+128. London: J. & A. Churchill Ltd. 1948. Price 8s. 6d. net.

This book is short and contains no illustrations, yet it makes excellent reading. The aim of the author has been to provide simple and easy reference for information concerning affections of the breast. It should prove especially helpful to the General Practitioner, who is confronted so frequently with breast conditions.

*A History of the American Medical Association, 1847-1947.* By MORRIS FISHBEIN, M.D. Pp. 1226. London: W. B. Saunders Company. 1948. Price 50s.

The American Medical Association has done well to mark the hundredth year of its existence by the publication of this handsome volume. Nathan Smith Davis was the founder of this society, and, as is most fitting, the story opens with a short

biography of this worthy man, who was born in a log cabin, and whose long life of eighty-seven years is a noble record of public service. He was only thirty years of age when he founded the Association, and he still had some years of useful work ahead of him when, at the age of sixty, he became the first editor of the *Journal of the Association*. The inaugural meeting took place at Philadelphia on 5th May 1847. There was the usual discussion regarding a suitable name, and then the Association concerned itself with more serious matters, such as the fight against quackery, the establishment of a code of ethics, and the organisation of the medical profession throughout the vast American continent. Thus closely identified with every phase of medical activity and progress, the Association grew rapidly, and its history, now so clearly and attractively presented, is virtually the history of American Medicine during the past century. An organisation so large and influential demanded leaders of ability and eminence, and the biographies of the distinguished Presidents, which constitute the second half of the volume, testify to the very high standard of American Medicine and Surgery. Dr Fishbein, the present editor of the *Journal*, is to be congratulated on the publication of this stimulating account of the evolution and progress of the world's largest medical society.

*Introduction to Medical Psychology.* By L. ERWIN WEXBERG, M.D. Pp. viii+171. London: William Heinemann (Medical Books) Ltd. 1948. Price 17s. 6d.

The medical student applying himself for the first time to the study of the mind is apt to be overwhelmed by the subject, and it is agreed that some knowledge of normal psychology is desirable before the study of psychiatry is taken up. Most textbooks on psychology are too full and detailed for the medical student, so Dr Wexberg has written a short yet comprehensive account of the subject which keeps in mind the requirements of the practitioner of medicine. The book is excellently produced and should be of the greatest assistance to the undergraduate.

*Breast Feeding.* By F. CHARLOTTE NAISH, B.A., M.B., B.CH. (CANTAB.). Pp. xii+151, with 20 illustrations. London: Oxford University Press. 1948. Price 10s. 6d. net.

This "Guide to the Natural Feeding of Infants" written by a mother of five children who is also a general practitioner is a notable and timely contribution in these days of waning enthusiasm for breast feeding. It is based on the Sir Charles Hastings Clinical Prize Essay awarded to Dr Naish by the British Medical Association.

The physiology of lactation and the management of breast feeding in varying circumstances are clearly and simply described, and the authoritative chapter on "The Mind of the Mother" is praiseworthy.

Breast feeding would receive a much needed impetus if this book were read by all concerned with infant care.

*Bilharzial Cancer: Radiological Diagnosis and Treatment.* By MAHMOUD AHMED AFIFI, M.B., CH.B. (CAIRO), M.R.C.S. (ENG.), L.R.C.P. (LOND.), D.M.R.E. (CANTAB.). Pp. vii+111, with 60 illustrations. London: H. K. Lewis & Co. Ltd., Price 16s.

The author opens with a discussion on the incidence of malignant neoplasm in relation to bilharzial infections with details of the chief organs affected. He shows, from hospital records, that the most frequent site is in the bladder.

The second section deals with the author's researches into the radiological diagnosis not only of bilharziasis, but also of carcinoma and the points of distinction. This part is supported by selected case histories and numerous illustrations.

The third section is devoted to treatment. Cases are classified according to the treatment indicated, by radium or deep X-ray therapy, curative or palliative. Details of technique are given.

The author has summarised in this small but attractive volume the result of twenty-five years experience in the diagnosis of carcinoma secondary to bilharziasis in a manner likely to be of considerable value to those working in the same field.

*Modern Trends in Ophthalmology.* Edited by ARNOLD SORSBY. Volume II. Pp. xix+600, with 546 illustrations and 3 coloured plates. London: Butterworth & Co. Ltd. 1948. Price 63s. net.

At the present time the general tendency in medicine is towards increasing elaboration of instruments and technique for examination, diagnosis and treatment. The second volume of this work well exemplifies this tendency in ophthalmology and will be welcomed by ophthalmic surgeons who are specially interested in its more scientific aspects, though it also contains much of interest to clinicians. The subject is presented in five sections:—Physiology, Diagnosis, Pathology, Treatment and Social Aspects, which are dealt with in forty-eight articles, five by the editor and the others each by a different author. Twenty-one papers come from British sources, nine from the U.S.A., and the remainder, with the exception of a Chilean contribution, from Europe and Russia. The book gives, therefore, a fairly good conspectus of the progress of ophthalmology all over the world. Many of the essays are interesting and informative though here and there it may be thought that more investigation and experience are required before the views expressed can become incorporated into practice. An elaborate and complicated method for the intracapsular extraction of cataract is described but the forceps extraction of the intumescent lens is dismissed in two lines as impossible. No reference is made to the local application of sulphonamides in powder form and the article on glaucoma without hypertension seems rather *vieux jeu* for a "modern trend." The book is in some respects more conservative and less bold than it might be but it will be valued as a supplement to existing textbooks. It is well got up and both illustrations and index are excellent.

*Sexual Behaviour in the Human Male.* By ALFRED C. KINSEY, W. B. POMEROY, and C. E. MARTIN. Pp. xv+804. London: W. B. Saunders Co. Ltd. 1948. Price 32s. 6d.

This is not just another of these books but a serious and scientific study of the many problems involved. Dr Kinsey, who is professor of zoology in the University of Indiana, has been investigating the subject for six years under the auspices of the National Research Council's Committee for Research on Problems of Sex and with the help of funds from the Rockefeller Foundation.

The investigation dealt with some thousands of persons and the data have been mathematically treated in great detail. Dr Alan Gregg in his preface describes the studies as "sincere, objective, and determined explorations of a field manifestly important to education, medicine, government, and the integrity of human conduct generally."

*Tuberculosis in Young Adults: Report on the Prophit Trust Survey 1935-44.* By MARC DANIELS, FRANK RIDEHALGH, V. H. SPRINGETT and I. M. HALL. Pp. xvi+227, illustrated. London: H. K. Lewis & Co. Ltd. 1948. Price 30s. net.

The problem of tuberculosis in young adults is not new. It has been accentuated by the war and there is no convincing explanation of why the disease falls so heavily on this young group. It is a problem which is full of difficulties, not the least of which is the relation of the established disease to the previous primary infection. This survey was started in 1934 and terminated in 1944, and in that time more than 10,000 presumably healthy young adults were examined and followed up. It yielded results of great interest bearing on the incidence of tuberculosis infection: on changes in tuberculin sensitivity: on the incidence of tuberculous disease: on morbidity rates and the incidence of tuberculosis during the survey: on the prognosis of the early

lung lesion and on the vexed question of its pathogenesis. The planning of the survey was the work of organising committees, and the survey itself was carried out by the four authors during their tenure of Proffit Scholarships. The report should be studied by all who are responsible for the handling of the problems of tuberculosis.

*Modern Trends in Diagnostic Radiology.* Edited by J. W. McLAREN, M.A., M.R.C.S., L.R.C.P., D.M.R.E. Pp. xxi+464, with 381 illustrations. London: Butterworth & Co. Ltd. 1948. Price 6os. net.

This volume forms a notable addition to the Modern Trends Series. It is not a systematic textbook, but a collection of over thirty articles contributed by workers well known in their own particular speciality. A pleasing feature is the number of contributions from continental writers. The articles are for the most part well illustrated and accompanied by a valuable bibliography.

Diagnostic radiology covers such an enormous field that the choice of subjects must have been no easy task. Omissions have been inevitable and it is certain that no selection would meet with universal approval. Some criticism, however, would appear to be justified. For example, there are more pages devoted to consideration of tumours of the pharynx and larynx than to the whole of gastro-enterology, and the œsophagus is somewhat surprisingly omitted. There is an excellent article on kymography, but no account of tomography. The article on radiology of the heart is disappointingly short, particularly the section on congenital heart disease, which surely merits more generous treatment in view of its present day importance.

Notwithstanding these criticisms this book should be of considerable interest to the clinician as well as to the diagnostic radiologist.

*Lecture Notes on Pharmacology.* By J. H. BURN, M.D., F.R.S. Pp. viii+128. Oxford: Blackwell Scientific Publications. 1948. Price 6s.

This small book provides a summary of the material needed for examination purposes. This material is very concisely and clearly presented so that the book is very easily read and digested. It should prove to be most useful if read in conjunction with a larger textbook which will provide more detail.

*The Psychology of Behaviour Disorders.* By NORMAN CAMERON, M.D., PH.D. Pp. xxi+662. London: H. K. Lewis & Co. Ltd. Price 25s. net.

This is an interesting book which accomplishes what it sets out to do—namely, to give a bio-social interpretation of behaviour disorders which may or may not amount to what we know as insanity. The chapters dealing with Personality Development and Behaviour Disorders, and with the principles underlying psychological adjustment are especially valuable. It is refreshing to read a book in which the author presents his views so clearly and constructively. It can be recommended without any reservation.

*Management in Obstetrics.* By ANDREW M. CLAYE. Pp. vii+194, with 17 illustrations. London: Oxford University Press. 1948. Price 12s. 6d. net.

This small volume is written for general practitioners. There are chapters on such essential subjects as ante-natal supervision, breech delivery, etc., but a chapter each is devoted to the practical problems of episiotomy, failed forceps, resuscitation, on calling in consultants and instructions on masks. The limitations of domestic midwifery are indicated where the services of a maternity hospital are available.

The author's ample experience and personal practice determine the form of management and treatment advised and described. There is no discussion of the merits of alternative methods. Of special value are the hints as to the tactful handling of patients and situations. Practitioners will find much sound teaching clearly set forth on the part they should play in the modern obstetrical team.

## NEW EDITIONS

*Psychology of Personality.* By ROSS STAGNER. Second Edition. Pp. xiii+485  
London: McGraw-Hill Publishing Company Ltd. 1948. Price 30s. net.

This book aims at giving a scientific study of personality, of how it can be measured, and of its development. It is informative and instructive but is inclined to be rather too dogmatic. The author's dream of seeing the development of mature personalities, immune to propaganda for hate and fear—free personalities in a free society—is an ideal which for the most part is unattainable. It will take thousands of years before any material progress along such lines will be made. A book of this type has a very limited usefulness.

*Minor Surgery.* By R. J. MCNEILL LOVE, M.S. (LOND.), F.R.C.S. (ENG.). Third Edition. Pp. vii+430, with 221 illustrations. London: H. K. Lewis & Co. Ltd. 1948. Price 22s. 6d. net.

This concise and readable manual contains much that will be of value to the young surgical resident and to the practitioner who may have to deal with minor surgical problems. A wide field is covered and practical descriptions of the common minor surgical procedures are given. Each section is adequately illustrated, particularly those dealing with fractures and dislocations.

*Tuberculosis in Childhood.* By DOROTHY S. PRICE, M.D. Second Edition. Pp. 228, with 54 plates. Bristol: John Wright & Sons Ltd. 1948. Price 25s. net.

The second edition of this book on tuberculosis in childhood will be welcomed by the tuberculosis physician, the pædiatrician and the general practitioner alike. The text has been revised in the light of recent advances and contains many useful references. The radiographs are well chosen and well produced. The chapters on extra-pulmonary tuberculosis are necessarily brief, but serve to emphasise the pathogenesis of tuberculous infection which is the basis of the author's clinical approach to the disease. The author has had extensive experience in childhood tuberculosis and the book is written with authority and bears the stamp of individual thought and study.

*Recent Advances in Anaesthesia and Analgesia.* By C. LANGTON HEWER, M.B., B.S., M.R.C.P., D.A. Sixth Edition. Pp. viii+380, with 149 illustrations. London: J. & A. Churchill Ltd. 1948. Price 21s.

In spite of a quick succession of editions this latest one is fully justified by the considerable volume of fresh material which has been included. Additions to the text cover new agents, apparatus and other developments associated with anæsthetic practice. Electro-narcosis, resuscitation and the use of specific muscular relaxants are among the many subjects considered. The latter have been selected and discussed with the author's well-known capacity for discriminating analysis and assessment. Many good illustration, much improved quality of paper and a high standard of production are all worthy features of this indispensable work of reference.

*Clinical Diagnosis by Laboratory Methods.* By JAMES CAMPBELL TODD and ARTHUR HAIRLEY SANDFORD. Eleventh Edition. Pp. xi+954. London and Philadelphia: W. B. Saunders Company. 1948. Price 37s. 6d. net.

The edition has been completely revised to bring it up to date with the advances that have taken place in medicine during the past five years. The section on sero diagnosis has been re-written and divided into three full yet concise chapters. A chapter on fungi and their classification has been added to this edition together with

many valuable illustrations. The hæmotological illustrations are extremely good and deserve special mention.

This textbook should prove of great service to both clinician and pathologist alike.

*Chest Examination.* By R. R. TRAIL, M.C., M.A., M.D., F.R.C.P. Third Edition. Pp. xi+172, with 115 figures. London: J. & A. Churchill Ltd. 1948. Price 12s. 6d.

Physical examination of the chest is still of great value to one who has troubled to acquire the art, though there is an increasing tendency to rely upon radiological help. The author from his great experience has set himself the task of correlating physical signs with radiological findings in diseases of the lungs.

The earlier part of the book deals with fundamental principles, the later with applied pathology. It should be very useful to both practitioner and student alike.

*Correlative Neuro-anatomy.* By JOSEPH J. McDONALD, M.S., M.Sc.D., M.D., JOSEPH G. CHUSID, A.B., M.D., and JACK LANGE, M.S., M.D. Fourth Edition. Pp. 146, with 60 illustrations. California: University Medical Publishers, Palo Alto. 1948. Price \$3.00.

This book is divided into three sections. The first deals with the anatomy of the cranial nerves, spinal nerves and the autonomic system. The illustrations in this section are excellent, and in discussing each nerve such subjects as lesions affecting the nerve and the symptoms and signs arising from these lesions are considered. The second deals with the subject of diagnosis and again is presented largely from an anatomical angle. The third discusses individual diseases of the nervous system, and this section has been completely revised in this edition.

The book should prove useful to those learning the subject of neurology who like their knowledge in tabulated form.

*Clinical Laboratory Methods and Diagnosis* (3 volumes). By R. B. H. GRADWOHL. Fourth Edition. Pp. 3263, with 58 plates and 1111 figures. London: Henry Kimpton. 1948. Price £10, 10s. net.

A reference book of this size leaves the laboratory worker with a sense of awe and perhaps some despair at his own inability to cope with all the numerous branches of science into which it delves. At the same time, one cannot fail to marvel at the perseverance and meticulous care with which the author (assisted by Professor Kouri) has marshalled such a vast array of laboratory methods and procedures.

Volume I is mainly devoted to biochemistry and hæmatology but also deals with blood transfusion and sundry miscellaneous chemical methods. Volume II deals with bacteriology and serology and sections are devoted to forensic chemistry, basal metabolism and electrocardiography. Volume III covers protozoology and helminthology. In short, it deals with all laboratory procedures with the single exception of radiology. Here we may read a detailed description of how to mount museum specimens, or choose one of the eight methods for the determination of blood urea, or be fascinated by a very full account of the activities of the Black Widow Spider.

But these volumes are not simply a conglomeration of practical details; there is a considerable amount of theoretical discussion, and the relative values of the various investigations are critically analysed. The several tests of renal function, for instance, are very fully compared and evaluated. When debatable points crop up, references are given to the original literature so that the book is doubly valuable as a means of reference.

If one might dare to refer to omissions in a work of such a size, the reviewer thought it peculiar that no reference is made to the manometric apparatus of Van Slyke and all its various uses.

The book is well illustrated with numerous coloured plates and photographs. The index is a work of art.

*Diseases of the Skin.* By OLIVER S. ORMSBY, M.D., and HAMILTON MONTGOMERY, M.D., M.S. Seventh Edition. Pp. 1462, with 764 illustrations and 11 coloured plates. London: Henry Kimpton. 1948. Price 90s. net.

When a book has reached its seventh edition it does not require much reviewing and this book is no exception to the general rule. The authors have brought it up to date by the inclusion of newer remedies such as streptomycin, and the treatment of syphilis with penicillin. Increase in size has been avoided by the omission of out-of-date material and by the use of smaller type in places.

The reviewer has long held that terminology is the curse of dermatology and in consequence he is glad that the authors have not adopted the terms which some writers would use though they mention some of these terms in one section. They have, however, a rather irritating habit of using different terminations for their adjectives, sometimes employing the neuter termination and at others the feminine although attached to the same noun, e.g. xeroderma pigmentosum and xeroderma pigmentosa. At other times they employ the feminine adjective with a neuter noun, while "sulphur" is sometimes used and "sulfur" at others. Uniformity is desirable and the definite lack of it in this respect is rather a blemish in a book of this size.

The authors state that the usual carcinoma in xeroderma pigmentosum is basal cell and less frequently squamous cell. This is contrary to the usually accepted view that these cancers are squamous epitheliomata.

As in former editions the illustrations are numerous and excellent.

## BOOKS RECEIVED

- AIRD, IAN, CH.M., F.R.C.S. *A Companion in Surgical Studies.*  
(*E. & S. Livingstone Ltd., Edinburgh*) 63s. net.
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(*Bailliere, Tindall & Cox, London*) 44s. net.
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(*H. K. Lewis & Co. Ltd., London*) 21s. net.
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(*Longmans, Green & Co., London*) 25s. net.
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(*E. & S. Livingstone Ltd., Edinburgh*) 25s. net.
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(*Staples Press Ltd., London*) 15s. net.
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(*John Wright & Sons Ltd., London*) 52s. 6d.
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(*Bailliere, Tindall & Cox, London*) 42s. net.
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(*Oxford University Press, London*) 30s. net.
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(*Eyre & Spottiswoode (Publishers) Ltd., London*) 14s. net.
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(*Wm. Heinemann Medical Books Ltd., London*) 15s. net.
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(*Henry Kimpton, London*) £7, 10s. net  
2 Vols.
- WOOD JONES, FREDERIC, D.SC., M.B., B.S., F.R.S., F.R.C.S. *The Foot.* Second Edition.  
(*Bailliere, Tindall & Cox, London*) 25s. net.

# INCO-ORDINATE UTERINE ACTION IN LABOUR

By T. N. A. JEFFCOATE, M.D., F.R.C.S.E., F.R.C.O.G.

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INEFFICIENT uterine action has long been recognised as a cause of difficult labour, and the clinical picture is described with great accuracy by the older writers such as Smellie (1877). Yet despite all manner of clinical and experimental studies on uterine contractions, their disorders

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stands the test of time:— 1. Pain severe and general or local and cramped. 2. The intermission incomplete. 3. The pains often leave distressing uneasiness in the back. 4. The patient irritable, despairing, or even delirious." Very little has been added to this clinical picture since then and practically the only thing which is new is the phrase inco-ordinate uterine action, and even this compares unfavourably with the beautifully descriptive, although vague, terms used by older writers—lingering labour, laborious labour, spurious labour, tedious labour.

A term which has caused a good deal of confusion since the early years of this century is "uterine inertia," and if any proof of this be necessary it was provided at a meeting of the Section of Obstetrics and Gynaecology of the Royal Society of Medicine held in January 1948, when the four opening speakers gave different definitions and classifications of the condition. Clinical observation of cases of prolonged labour goes to show that inertia in the accepted dictionary sense of the word is not nearly so common as is generally supposed. If uterine muscle is inert, that is, inactive and atonic in all areas, and no pathological lesion such as retroplacental hæmorrhage is present, the patient should not experience any pain of uterine origin. Why then, in most of the cases diagnosed as inertia, does the woman feel discomfort of such a degree that it interferes with sleep and leads to mental if not physical exhaustion? Why does the standard treatment consist in the administration of analgesics and hypnotics? The presence of the pain

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and the need for sedatives implies uterine activity of some sort and its usual position low in the back suggests that a quiescent or feebly acting upper segment is merely a reaction to a lower segment and cervix which are offering resistance to dilatation. This argument receives support from Kreis (1934) and from Lorand (1936, 1947) Nixon (1948) and Reynolds *et al.* (1948) who by tocographic records have been able to demonstrate that many cases of inertia are characterised by high muscle tone, present especially in the middle and lower zones of the uterus. Although true hypotonic inertia does occur, the majority of cases are of the type described above and they represent disturbed polarity of the uterus, or inco-ordinate uterine action. This, however, is not the only type of inco-ordinate uterine action. Sometimes it appears as violent and irregular spasmodic contractions of the upper segment, the so-called "colicky uterus." These two conditions, however, are closely related and as Phillips (1938) has pointed out, may occur as alternating phases in the action of the same uterus. Other examples of disordered uterine action are "constriction ring" or "contraction ring" dystocia, and rigidity of the cervix which is not associated with previous injury or disease. Inco-ordinate uterine action can arise at any time in labour but this communication is confined to its manifestations in the first and second stages.

Without at this juncture attempting to differentiate between the types it can be stated that the over-all clinical picture of inco-ordinate uterine action is prolonged labour and slow dilatation of the cervix despite strong uterine contractions and an absence of gross disproportion. The pains are unusually distressing, and are most commonly felt predominantly in the back, although sometimes they take the form of severe abdominal colic. The pain of normal labour is only present when the intra-uterine pressure is raised from the resting level of 5 mm. Hg. up to the contraction pressure of 25 or 30 mm. Hg. (Torpín—quoted by Rucker, 1946). When the muscle is in spasm or high tone the interval pressure already approaches the critical level and pain is experienced at the very inception of a contraction, before the hardening is perceptible to the observer. Similarly the pain continues for some time after the muscle appears to relax and may remain in a milder form throughout the intervals. The contractions of the inco-ordinate uterus may be very frequent or may be irregular in strength and periodicity. Very often the patient is acutely conscious that they are ineffectual and that labour is not progressing as it should, so she tends to become anxious and to lose morale. Women who have experience of normal labour either before or after inco-ordinate labour can readily appreciate the difference in the type of "pains." Occasionally after a long and tedious phase of first stage pain the patient may feel a desire to "bear down" although the cervix is not fully dilated. This bearing down effort can be surprisingly strong but is misdirected and appears to arise as a result of spasm in the lower bowel. On one or two occasions I have seen women in whom the pain of labour is referred almost entirely to the rectum. This false bearing down sensation is of considerable practical importance

in that it often deceives the attendant who then not only allows the woman to exhaust herself further in fruitless efforts, but who may easily become committed to an attempt at forceps delivery before the time is ripe. The cervix may be unusually thick or may become excessively thinned, sometimes it is applied tightly to the presenting part, sometimes it hangs down loosely into the vaginal vault.

Inco-ordinate action, however, is only relative for it occurs in all degrees from the most severe down to the mildest, the latter being impossible to distinguish with certainty from what may be described as the less efficient forms of co-ordinated activity. Normal uterine contractions are now envisaged as commencing simultaneously at each utero-tubal junction, the waves passing downwards and inwards to meet in the middle line where they continue as one towards the lower part of the uterus. From the central contraction subsidiary waves pass in circular fashion around the uterus (Rudolph and Ivy, 1930, 1931; Ivy, Harman and Koff, 1931; Rudolph, 1935; Malpas, 1944). As might be expected on embryological grounds each half of the uterus acts to some extent as an entity and is under the separate influence of the autonomic nerves from its own half of the pelvis. Co-ordination of the action of each half of the uterus is therefore essential to the efficiency of the whole. This, however, is not enough and what is more important is a balance of action between the upper and lower portions of the uterus. Indeed as Reynolds *et al.* (1948) say, "cervical dilatation is the result of a gradient of diminishing physiological activity from the fundus to the lower uterine segment." The most efficient uterus is one showing moderately low tonus and strong contractions. Although normal uterine action follows a general pattern Murphy (1947) reports that each uterus produces its own individual tocographic record. This agrees with clinical observations for no two patients have labours identical in character and there are wide variations within normal limits. It would appear that just as other co-ordinated muscle movements such as walking are peculiar to the individual, so is the behaviour of the uterus in labour.

It was previously stated that the clinical picture of disorderly uterine action is prolonged labour in the absence of gross disproportion. At the risk of causing confusion it is now necessary to point out that disproportion, sometimes enough to obstruct labour but sometimes of moderate or mild degree, is commonly associated with this form of uterine dysfunction and appears to be a cause of it. For the purposes of this paper, however, it is proposed to leave out of consideration those cases in which faulty uterine behaviour is caused and overshadowed by gross disproportion, as well as those in which it is the result of intra-uterine manipulations and the injudicious use of oxytocic drugs. As a basis for discussion it is proposed to review two small series of cases occurring in (a) private practice and (b) the practice of a hospital which drains one of the poorest districts of Liverpool, during two years 1947-48. The study of a few carefully observed and well documented cases seemed more profitable than an analysis of a large number of incomplete hospital records. Any general observations

made, however, are based on clinical experience dating back over the years as well as the study of these particular cases. The duration of labour in these cases varied from twenty-four to one hundred and sixty hours and even in the latter the cervix was incompletely dilated when delivery was effected by cæsarean section. It will be seen, therefore, that only the most severe types of the disorder are included, those in which the diagnosis was beyond reasonable doubt.

TABLE I

Duration of labour in hours	24-35	36-47	48-59	60-71	72-83	84-95	96-107	108-119	120+
Private series (62 cases)	13 (6)	6 (4)	15 (4)	8 (4)	9 (2)	2 (0)	6 (1)	1 (0)	2 (2)
Hospital series (39 cases)	2 (0)	15 (5)	7 (1)	8 (4)	3 (0)	... ...	3 (1)	... ...	1 (1)

Figures in brackets denote the number of cases (35 in all) terminated by cæsarean section before full dilatation of the cervix.

### INCIDENCE

The incidence of moderate or severe inco-ordinate uterine action is best assessed by the hospital series, 39 cases in 6123 consecutive deliveries (0.6 per cent.) amongst women mainly of the lowest income grades. The condition is seen much more commonly in private practice but the figures are of little value because a large proportion of the cases were seen during emergency consultations, the indication for the consultation being the inefficient uterus. Also it is quite impossible to compare the findings of one writer with those of another since the diagnosis of the condition is arbitrary. Sackett (1941) for instance, reported a more than one per cent. incidence of cervical dystocia amongst labours in which the foetus presented normally, and Johnson (1946) recorded that over one per cent. of 10,000 hospital deliveries were complicated by constriction ring dystocia. It seems fair to comment that most observers consider these conditions much less common and the figures only go to show how much the diagnosis depends on individual opinions.

### AGE AND PARITY

Although nearly all writers (Munro Kerr, 1937; Rudolph, 1935; Rucker, 1946; Gilliatt, 1933; Goodall, 1934) agree that it is usually primigravidæ who suffer from disorderly uterine action, the general estimate of 50 to 75 per cent. appears to be too low. Indeed it is quite rare to see it, at any rate in a severe form, in multiparæ unless it has been precipitated by interference. Table II shows that apart from two women who had each had one early abortion, only 7 out of 101 women suffering from inco-ordinate uterine action were multiparous and in one of these the pregnancy was in one horn of a uterus didelphys, this horn not having previously been the site of implantation. The fact that it is a disease confined almost entirely to primigravidæ is not surprising in view of the fact that resistance of the lower segment

and cervix to dilatation explains the greater length of all first labours. Also in this connection may be mentioned Murphy's (1947) observation that labour in primigravidæ is characterised by higher tone but weaker contractions than in multiparæ. The effect of disproportion is to increase tone in primigravidæ whereas it increases the strength of the contractions in multiparæ.

Although inco-ordinate uterine action is reputed to be most common in elderly primigravidæ especially those of low fertility, the effect of age is often exaggerated and young women are commonly affected. So Munro-Kerr (1947) points out that a rigid cervix is by no means peculiar to elderly primigravidæ and Rucker (1946) found that the average age of women suffering from constriction ring dystocia was only two years above that of a control series of women having normal labours. It is easy to get a wrong impression from casual

TABLE II  
*Age and Parity*

Type of Cases.	Parity.	Less than 20 years.	20-24.	25-29.	30-34.	35-39.	40-44.	Over 45 years.	Total.
Private series :—									
Inco-ordinate uterus .	Primi-gravidæ	...	7 (13%)	17 (30%)	21 (38%)	9* (16%)	2 (4%)	...	56
	Multi-gravidæ	...	...	1†	1	3	1	...	6
All cases of pregnancy (549 consecutive)	Primi-gravidæ	6 (1%)	77 (14%)	199 (36%)	152 (28%)	95 (17%)	20 (4%)	...	549
Hospital series :—									
Inco-ordinate uterus .	Primi-gravidæ	5 (13%)	13 (34%)	13 (34%)	7 (18%)	...	...	...	38
	Multi-gravidæ	1	...	...	...	...	...	...	1
All cases of pregnancy (1000 consecutive)	Primi-gravidæ	131 (13%)	493 (49%)	287 (29%)	57 (6%)	28 (3%)	4	...	1000

\* Two of these patients had each previously had one abortion.

† This patient had a uterus didelphys and her one previous pregnancy had occupied the other horn.

clinical observations. Table II shows that although cases of inco-ordinate uterine action seen in private practice mostly occur amongst women aged 25-34, the same is true of all first pregnancies amongst the well-to-do patients. In hospital practice the age incidence of inco-ordinate uterine action is lower but this is explained by the fact that childbearing commences at a lower age amongst the community served by the particular hospital. The private practice figures again are weighted by the selection of cases and the hospital statistics are more reliable. They go to show that elderly primiparity tends to increase the chance of inco-ordinate uterine action, but only very slightly. This is all the more surprising because it has been repeatedly shown that elderly primigravidæ in general tend to have longer labours (Foderl, 1936; Nathanson, 1935; Tew and Kuder, 1938). This is partly because of resistance of the soft tissues and partly because there is an increased incidence of occipito-posterior positions (Nathanson, 1935; Tew and Kuder, 1938).

## RUPTURE OF THE MEMBRANES

The time of rupture of the membranes does not appear to influence directly the action of the uterus. This agrees with the observations of Rudolph (1935) and most other writers but is contrary to views of Johnson (1946) and of Kreis (1934) who believe that adherence of the membranes can hinder dilatation of the cervix. Disorderly action was seen before rupture of the membranes in 56 cases, after premature rupture of the membranes in 22 cases, whilst information on this point is doubtful in the remaining cases. Even when the membranes were unruptured the uterine disturbance was sometimes enough to cause embarrassment to the foetus and the old dictum that the foetus is safe so long as the membranes are intact was more than once proved incorrect. In all cases the uterine disturbance commenced before full dilatation of the cervix and in the majority was present almost from the onset of labour—if not before. Moreover, when inco-ordinate uterine action was already present, artificial rupture of the membranes did not have any beneficial effect. According to Nixon (1948) the opposite is true in hypotonic inertia.

## PRESENTATION AND POSITION OF THE FŒTUS

Although it does not much matter whether the foetus presents by the head or the breech, an association between posterior position of the occiput or transverse arrest of the head and faulty action on the

TABLE III

*Presentation and Position of the Fœtus*

	Private Series.	Hospital Series.
I. Cephalic presentation :—		
(a) Anterior position of vertex . . . . .	26	8
(b) Unrotated or malrotated posterior and transverse position . . . . .	30	31
(c) Position unknown . . . . .	5	...
II. Breech presentation . . . . .	1	...

part of the uterus has often been noted (Marshall, 1933; Maliphant, 1933; Munro Kerr, 1947; Rucker, 1946; Goodall, 1934; Stern, 1948; Drew Smythe, 1948, etc.) Moreover the malposition appears to be the cause of the uterine dysfunction. It is impossible to say how it acts; Caldwell Moloy and d'Esopo (1936) suggest that the foetal axis of descent may be concerned, but most others postulate faulty stimulation of the birth canal by the presenting part. It has sometimes been suggested that the failure of the head to rotate favourably is the result rather than the cause of uterine inefficiency, but there is a good deal of evidence against this. For instance, the malposition nearly always precedes the uterine disturbance and when it is corrected but not before, good uterine contractions return. So it comes about that a posterior position of the occiput can often be diagnosed from the character of the pains of labour and I have several

times encountered women doctors with personal experience of several confinements who during labour could tell when the foetal occiput was posterior and when it rotated to the front.

When the vertex presented with the occiput anterior, it was frequently noted that the head was high at the onset of labour possibly implying slight disproportion. There is, however, another possible explanation—the late engagement of the presenting part may be an indication of delayed and incomplete formation of the lower segment and might be regarded as the earliest sign of inco-ordinate uterus, present even before the onset of labour.

### RESULTS—MATERNAL AND FŒTAL RISKS

Prior to the introduction of the lower segment cæsarean operation, and more recently, of chemotherapy, inco-ordinate uterine action and

TABLE IV  
*Method of Delivery and Results*

Method.		Mother.		Child.		
		Survived.	Died.	Survived.	Neonatal Death.	Stillborn.
Spontaneous delivery . . . .	P	6	...	6	...	...
	H	16	...	15	...	1
Forceps delivery with or without rotation of foetal head	P	30	...	24	3	3
	H	8	...	8	...	...
Cervicotomy and forceps delivery	P	1	...	...	...	1†
	H	3	...	3*	...	1
Failed forceps, internal podalic version	P	1	...	...	...	1
	H	...	...	...	...	...
Failed forceps spontaneous delivery later	P	1	...	1	...	...
	H	...	...	...	...	...
Lower segment cæsarean section .	P	23	...	21	1†	1
	H	12	...	11	...	1
Total . . . . .		101	...	89	4	9

\* One set of twins. † Child died from gross malformation. ‡ Child macerated—died in labour, ? asphyxia  
P = Private series. H = Hospital series.

the associated prolongation of labour exposed both mother and child to considerable risk. Depending on the type and severity of the case, constriction ring dystocia for instance was particularly dangerous, the maternal mortality varied between 10 and 50 per cent. and the foetal mortality was between 40 and 80 per cent. (White, 1936; Rucker, 1946; Rudolph, 1935; Bourne quoted by Grafton, 1947; Bell, 1933). Nowadays the better general care of the woman in labour, caution over anæsthesia and above all a readiness to resort to cæsarean section late in labour, has altered the outlook. This is borne out by the results in this series in which no mother lost her life and the foetal loss by stillbirth and neonatal death was 13 (corrected to 12 by the exclusion of one case of malformation) out of 102 babies (approximately 12 per cent.).

This does not mean that the condition has ceased to have its dangers. Although none died, many women in this series were seriously ill and

there were cases of severe soft tissue laceration, shock and chloroform poisoning as well as of puerperal infection. Moreover, although not included in this series, I have seen at other hospitals within the last few years occasional fatalities and the greatest care is necessary if these are to be avoided. The risk to the foetus is primarily intra-partum asphyxia—the result of uterine spasm and raised intrauterine pressure which presumably interferes with the placental circulation—and secondarily birth injury associated with forcible delivery. It is likely that in these series practically all the babies delivered by cæsarean section would have been lost if more conservative treatment had been adopted. If this is so the foetal mortality, but for cæsarean section, would have been in the neighbourhood of 50 per cent., a figure which is similar to the one recorded for the past.

Although ordinarily there is little risk of spontaneous rupture of the uterus, ischæmic or pressure necrosis can involve small or large areas of the uterine wall, and one of the most interesting injuries of this type is detachment of all or part of the vaginal cervix, an accident for which the improper use of forceps has so often, but wrongly, been blamed. Without going into all the arguments for and against, it would appear that annular detachment is most likely to occur in true cervical dystocia, that is, when efficient expulsive contractions force the foetus strongly against a resisting cervix. So it is usual to find that labour proceeds quickly and delivery is relatively easy once the cervix becomes detached.

#### ULTIMATE HISTORY OF PATIENTS WHO SUFFER INCO-ORDINATE UTERINE ACTION

It is of some importance to know the ultimate effect on the child-bearing function of women who pass through the ordeal of the painful and exhausting labour associated with inco-ordinate uterine action,

TABLE V

##### *A. Forty-seven Cases Treated by Cæsarean Section*

Further conception avoided . . .	17 (36 per cent.)
? domestic reasons—1	
medical reasons—1	
Involuntary sterility (two years or more)	5
Further pregnancies . . . . .	25

##### *B. Forty-four Cases Treated by Forceps Delivery*

Further conception avoided . . .	16 (37 per cent.)
? domestic reasons—5	
Involuntary sterility (two years or more)	3
Further pregnancies . . . . .	25

for it may influence outlook on its treatment. In the hope of obtaining some information on this point a third series of hospital patients delivered during the years 1936-46 inclusive have been followed up. Only the most severe cases, those requiring cæsarean section or forceps delivery, were selected. There were 140 non-fatal cases, but 49 cannot be traced.

The striking feature of these figures is that irrespective of the mode of delivery, rather more than one-third of the women or their husbands, or both, decided that their labours had been such that further pregnancies should be avoided. In 6 of these cases housing and other domestic and personal factors also influenced the decisions. Indeed, only about one-half of the women had further children. It had been hoped that this enquiry might give some indication as to whether a labour of moderate length ending in cæsarean section is more disconcerting than a rather longer labour ending in forceps delivery, and as to which treatment is better from the standpoint of the ultimate size of the family. There is little difference in the figures but further analysis suggests the future outlook of the patient is influenced more by the fate of the child than the type of treatment. With the exception of one who was separated from her husband, all the women who lost their first child tried to conceive again; all those

TABLE VI

Mode of Delivery in Second Pregnancy.	Cæsarean Section in First Pregnancy.	Forceps Delivery in First Pregnancy.
Still undelivered . . . . .	1	...
Abortion . . . . .	2	1
Spontaneous delivery . . . . .	3	20
Forceps delivery . . . . .	2	2
Elective cæsarean section . . . . .	12	2
Trial labour followed by cæsarean section . . . . .	5	...
Total patients . . . . .	25	25
Total of subsequent pregnancies amongst all patients at time of follow-up	28	33

who avoided conception had a living child. One or two women only embarked on pregnancy again on being promised that subsequent delivery would be by elective cæsarean section.

In those cases where a further pregnancy occurred the outcome is also of some interest and the details are shown in Table VI.

Those women whose first labour ended in forceps delivery nearly all had a spontaneous delivery of a live child in the next, and moreover, the second labour usually proceeded easily and quickly. Of those who had cæsarean section 12 had a repeat operation without the uterus being put to the test. Ten women were allowed to go into labour again and of these half required cæsarean section again. However, of these latter 5 only 2 had a real trial labour, the remainder being three, four and twelve hours in labour only. The implication is that in a large proportion of cases the behaviour of the uterus is much more efficient in the second labour and that whereas cæsarean section may be necessary in the first labour there is a good chance of vaginal delivery in the second. This also is borne out by the findings in the few cases amongst the private series where the further history is known. Of 5 who had cæsarean section at the first labour and conceived again, 2 had elective cæsarean operations, 2 were delivered per vaginam and the remaining one had a repeat cæsarean section carried out soon



after the onset of labour—not because of faulty uterine action but because of suspected prolapse of the cord. Of 10 women delivered initially with forceps after difficult labour, all had easy second labours and 9 delivered themselves spontaneously, the remaining one having a simple low forceps extraction. These isolated observations are added to the findings shown in Table VI to give the figures in Table VII.

Women who had *cæsarean* section in the first labour and forceps delivery in the second, usually achieved spontaneous delivery in the third. This might be described as being the typical history. Uterine action improves with each labour and when *cæsarean* section is performed in the first the outcome of the second is largely dependent on the degree of dilatation of the cervix at the time of operation. If it is less than half dilated *cæsarean* section may be necessary again the next time despite the fact that the cervix attains further dilatation. If, however, the cervix is half or more dilated the first time, there is a good chance it will reach full dilatation in the next labour. Once the cervix has been fully dilated and even though delivery is only effected with difficulty and with death of the child, subsequent deliveries

TABLE VII

Mode of Delivery in Second Pregnancy.	<i>Cæsarean</i> section in First Pregnancy.	Forceps Delivery in First Pregnancy.
Spontaneous delivery . . . . .	3	29
Forceps delivery . . . . .	4	3
Elective <i>cæsarean</i> section . . . . .	14	2
Trial labour followed by <i>cæsarean</i> section	6*	...

\* Less than twelve hours trial of labour in 3 cases, *cæsarean* section being then carried out for indications other than faulty uterine action.

are usually easy. This natural tendency for the uterus to function better in subsequent pregnancies has also been noted by Rucker (1946) in connection with constriction ring dystocia and by Stern (1948) in cases of inertia. It also coincides with everyday observations on normal labour. It should influence judgment in regard to treatment, yet it is frequently overlooked and this not only in regard to the repetition of *cæsarean* section. How often is it decided to carry out an elective *cæsarean* operation for a bad obstetric history which consists in no more than an inco-ordinate labour ending in a difficult forceps delivery of perhaps a stillborn child? It ought too, to play a prominent part in the propaganda necessary to prevent a woman being deterred from further childbearing by a long and tedious labour. Such women can be promised with a fair degree of confidence that their next labour will be of a very different character. Patients who have been followed up and questioned often made a point of emphasising that the nature of the pains and their sensations and reactions were different in the second as compared with the first labour.

#### SOME EXPERIMENTS IN TREATMENT

It is not proposed to deal with the standard treatment of inco-ordinate uterine action except to express the opinion that the administration of

analgesics and anti-spasmodics, and especially morphia and pethidine, in adequate doses at the first sign of uterine inefficiency and repeated liberally, remain the first and best line of attack. Some comment on other methods of treatment which have been tried, albeit unsuccessfully, may however, be of interest. Intravenous injections of magnesium sulphate as advocated by Abarbanel (1945) and others (Annotation, *Brit. Med. Journ.*, 1945) were tried in two cases of colicky uterus without obvious effect, but in one case of hypertonic lower segment it appeared to promote rapid dilatation of the cervix. Trinitroglycerine was given to one patient, and prostigmine to two others, without benefit. Œstrogens in the form of stilbœstrol or œstradiol benzoate were employed in 15 cases without obvious improvement in uterine function. Although œstrogens may sometimes appear to be of value in cases of hypotonic inertia (Jeffcoate, 1938) and Murphy's (1947) tocographic records show that they apparently can raise tone, it is difficult to substantiate their use on theoretical grounds mainly because it is unreasonable to expect any uterine response in less than ten hours after the first administration. This is true even when they are given intravenously (Reynolds, 1933), and œstradiol benzoate in propylene glycol administered intravenously in large doses, mostly 125 mgms. and once 500 mgms., at a time, do not in my experience have any constant immediate effect on either the hypotonic or hypertonic uterus. Another experimental form of therapy which deserves mention is the continuous intravenous infusion of extremely dilute solutions of oxytocin in glucose saline as recently advocated by Theobald and others (1948) for uterine inertia. In cases of hypotonic inertia an oxytocin "drip" undoubtedly gives good and sometimes dramatic results and seems reasonably safe because it is easily controlled. If, however, it is given to cases of hypertonic inertia, or more strictly, inco-ordinate uterine action, the effect is far from beneficial. We tried it in two cases only and the almost immediate effect was that the patient suffered the most severe pain—still of inco-ordinate type. Indeed, she became so distressed that the drip had to be discontinued after a very short time. Clinical and experimental evidence (Reynolds, 1930; Murphy, 1947; Reynolds and others, 1948), goes to show that contrary to the original statement of Blair-Bell (1909) oxytocin does not change the quality of uterine action, its effect depending on the degree of tone and activity already present. It intensifies both normal and abnormal contractions alike. It can be a cause of inco-ordinate uterine action, or at least it can light up a latent condition, and it certainly has no place in the treatment of this disturbance. The most careful diagnosis and differentiation between hypertonic and hypotonic states is necessary before it is administered for what appears to be uterine inertia.

Bearing in mind the general view that inco-ordinate uterine action is often brought about by an over-active sympathetic nervous system, it seemed reasonable to try treating patients with tetra ethyl ammonium chloride, which is alleged to paralyse sympathetic nerve ganglia. It was given in 11 cases—in two of which a constriction ring was present as proved by subsequent cæsarean section. In each case the initial

dose (intravenous) was 0.25 or 0.3 gm. and this was repeated a variable number of times, the largest amount given to one patient being 1.5 gm. in the course of nine hours. It produced the usual reaction of fall of blood pressure, metallic taste in the mouth and visual disturbances, all of which passed off within half to one hour. In every case it appeared to bring on an almost immediate strong and sustained contraction—so sustained in one case as to cause alarm for the foetus. The uterus then continued to contract rather more strongly and sometimes more frequently, for a varying period up to one hour after the injection. However, there is no convincing evidence that it altered the character of the contractions: in some cases they clearly remained inco-ordinate, the two constriction rings persisted, and except in possibly one case dilatation of the cervix was not obviously facilitated. The over-all effect on the progress of inco-ordinate labour has been disappointing. It is difficult if not impossible to interpret the experiments. If it is true that this drug paralyses or reduces the activity of the sympathetic—there is some evidence that its effect is not always reliable (*Annotation, Brit. Med. Journ.*, 1948)—and if the dose employed was adequate, then our observations do not support the contention that over-activity of the sympathetic causes disorderly uterine action. Nevertheless the drug does have some influence on the uterus, as is evidenced by the strong contractions noted in every case.

#### THE PART PLAYED BY NERVOUS AND EMOTIONAL FACTORS IN CAUSING INCO-ORDINATE UTERINE ACTION

Anxiety and nervousness have been recognised causes of inefficient uterine action by many generations of obstetricians. Most authorities agree that they play a significant part in the aetiology of both inertia and inco-ordinate action. Clinical experience tends to bear this out and, for this reason, doctors' wives and nurses—those with dangerously little knowledge—appear to be especially prone to these disorders. A state of tension, often subconscious, is said to be associated with high tonicity and resistance in the lower segment and cervix. Read (1947) carries the argument so far as to say that if this tension can be excluded completely, uterine action is so smooth as to be virtually painless. Linked up with this outlook is the recent move to educate women during the ante-natal period and to teach them mental as well as physical relaxation. The exact mechanism whereby emotional and psychological factors influence uterine function is unknown, but the most likely is by sympathetic nerve impulses or by adrenalin liberated from the suprarenal, either of which tend to inhibit dilatation of the cervix and lower segment. Resistance to dilatation and the occurrence of spasm which are so characteristic of inco-ordinate uterine action can therefore be looked upon as evidence of an over-active sympathetic system. This theory is both attractive and popular and is supported by a good deal of evidence of all kinds. It is one to which I have subscribed in the past (Jeffcoate, 1948) but there is good reason to question it. The disappointing results obtained with tetra-ethyl ammonium chloride may or may not be significance. More important

is the fact that the theory does not satisfactorily account for the relationship between disorderly uterine action and parity. It is said that this condition is mostly seen amongst primigravidæ because they "fear the unknown." I would submit, however, that any primigravida who experiences inco-ordinate uterine action finds labour more distressing than even her worst fears led her to expect and she is therefore likely to be even more apprehensive over her second confinement. This is certainly true in some cases and much reassurance is necessary, and even then distrust remains. Yet no matter whether reassurance is successful or not, uterine function is nearly always good in the second labour. The cervix and perhaps the lower segment as well, behave as passive rather than active muscle tissues and once they have been stretched, never return to their previous state. In this connection Goerttler's views (Kreis, 1934; Jacob, 1935) on the structure and method of dilatation of the cervix and lower segment deserve mention. There is no need to elaborate this argument and it suffices to say that the time is ripe for a reassessment of rôles played respectively by a neuromuscular disturbance and an unnatural mechanical resistance of the soft tissues of the lower part of the uterus.

#### SUGGESTED CLASSIFICATION OF TYPES OF INCO-ORDINATE UTERINE ACTION IN LABOUR

By way of conclusion and summary it is proposed to put forward a tentative classification of disorderly uterine action, one which attempts to reconcile most of the clinical and experimental observations recorded in the literature. To some extent it is speculative, but it may be of some value if only as a working basis.

##### *Classification of Inefficient Uterine Action*

- I. *Inertia*.—Hypotonic uterus, ? normotonic uterus.
- II. *Inco-ordinate uterine action*—
  - (a) Resistant lower segment (hypertonic and ? normotonic "inertia," reversed polarity).
  - (b) Colicky uterus (spasmodic action of upper segment):  
Asymmetrical uterine action.
  - (c) Spurious labour.
  - (d) Constriction ring dystocia (contraction ring).
  - (e) ? cervical dystocia (achalasia of cervix).
- III. *Cervical dystocia*—
  - (a) Idiopathic (rigid cervix, conglutination of external os).
  - (b) Resulting from disease or previous injury of the cervix.

##### *I. Inertia*

This term should be restricted to those cases in which the uterus is inactive or only feebly active in all areas. It is characterised by low tone in the lower segment as well as other areas. The patient experiences no pain or only slight pain of a normal distribution during a weak contraction.

##### *II. Inco-ordinate Uterine Action*

(a) **RESISTANT LOWER SEGMENT**.—This probably represents the commonest type of what is ordinarily called inertia and is characterised

by feeble action of the upper segment which is associated with and is probably secondary to a hypertonic low or middle zone of the uterus. It is open to argument as to whether normotonic inertia should be included in this group or with true inertia. The patient's predominant sensation is backache. Characteristically the sensation of pain precedes and outlasts a palpable contraction, as it does also in the other forms of inco-ordinate action. In general it can be stated that the worse the backache in labour, the less efficient the uterus. In normal labour backache is not a prominent feature except possibly towards the end of the first stage. There may also be rectal and colonic spasm and false bearing down pains. Sometimes spasm of the lower bowel is reflected in distension of the colon and this may displace the uterus to one side or give the impression of obliquity of the uterus. This state of affairs in which the upper segment is quiescent and the lower segment is over-active is sometimes referred to as reversed polarity, a phenomenon which has been observed to occur spontaneously in monkeys and has been induced in these animals by stimulation of the hypogastric nerves (Ivy *et al.*, 1931).

(b) COLICKY UTERUS.—Here the upper segment contracts spasmodically and often irregularly and its action is not expulsive. The foetus is not therefore driven down on to the cervix, nor is the latter pulled open. During a contraction the patient experiences intense pain and this persists to some extent between contractions. The muscle is in high tone. The pain is colicky and hypogastric if the upper part of the uterus is involved. If backache occurs as well it indicates some spasm in the middle or lower zone of the uterus. Sometimes the pain becomes almost incessant and excruciating. Colonic and rectal spasm may also occur as in the previous group.

*Asymmetrical Uterine Action.*—Each half of the uterus develops separately and has its own innervation and under certain circumstances it can act independently of its fellow. This is occasionally seen not only in the bicornute uterus but in the apparently normally developed uterus. When it does occur the action of one-half tends to be colicky and the clinical picture is the same as that of the colicky uterus except that there is a unilateral distribution of the pain. Unequal activity of the two sides of the uterus may be apparent on palpation and this again may give rise to the appearance of obliquity of the uterus during a contraction.

(c) SPURIOUS LABOUR.—The backache which often precedes labour by some days is evidence of resistance in the lower segment (Kreis, 1934), during the "taking up" process. It is sometimes a warning that labour will be complicated by a continuance of the resistance. In such cases it is extremely difficult to determine the onset of true labour and an error in this respect can lead to an underestimate of the seriousness of a patient's condition. False labour is also seen in the form of strong and painful contractions which are inco-ordinate in that they do not dilate the cervix. These contractions are quite strong although disproportionately painful and one characteristic is that they occur regularly and frequently, the frequency remaining the

same from the very outset. The pain is hypogastric in site or girdle-like and according to Goodall (1934) is sometimes referred to the thighs as in dysmenorrhœa. In spurious labour the behaviour of the uterus fundamentally resembles that of either group (a) or (b).

(d) CONstriction RING DYSTOCIA.—This is a well recognised clinical entity although it is not so common as some writers suggest. Although it can arise suddenly following some unusual stimulation, its spontaneous occurrence can be regarded as the end result of a colicky uterus (Phillips, 1934). It is in fact the same condition in an extreme degree and in which the spasm assumes an annular distribution. It occurs mostly at the junction of upper and lower segments but also in the upper segment. Its occurrence in the lower segment, and above all in the cervix, remains extremely doubtful despite the observations of Rudolph (1935), Rudolph and Ivy (1930, 1931). They as well as others describe it in the region of the internal os in which case they regard it as an atavism in that there is a sphincter at this level in bitches. Furthermore according to their view, a rigid cervix can be regarded as a constriction ring involving the external os. A constriction ring in the upper segment tends to produce abdominal pain; at lower levels, backache. The uterus never ruptures spontaneously as a result of a constriction ring and if the ring is above the level of the cervix, the cervix is thick and hangs loose in the vaginal vault, not applied to the presenting part.

### III. *Cervical Dystocia*

The condition of rigid cervix, achalasia of the cervix, or conglutination of the external os, as it is variously called, is the most difficult to place in the classification. Indeed there may be more than one condition covered by these various titles. It should be made clear that those cases in which the cervix is rigid because of disease or previous injury are excluded from consideration here. In the others all the evidence goes to show that it is impossible to demonstrate departures from the normal histological structure. To explain the failure of the cervix to dilate in these cases some postulate a functional disturbance of the neuro-muscular mechanism and regard the condition as analogous to a constriction ring or at least as an extension of a resistant lower segment. The difficulty about accepting such views and even of accepting the statements that the cervix is felt to contract during the examination, is that the cervix contains a minimal amount of muscle. This has long been recognised, and was emphasised in 1928 by Mathieu and Schaffer and again more recently by Danforth (1947) and by Schwarz and Woolf (1948). The external os, which is the usual site for dystocia, is virtually devoid of muscle. If these observations are correct the cervix is to be regarded merely as the tendon of the uterine muscle and its normal dilatation or its failure to dilate under certain circumstances can only be explained on the basis that its tissues are passive. It is tempting to postulate that just as other fibrous and fibromuscular structures within and around the pelvis become softened and relaxed by the influence of the hormonal conditions

of pregnancy, so does the cervix. The easy dilatation of the cervix is then dependent not only on efficient muscular activity on the part of the upper segment but also on the preparation of the cervix by relaxin or whatever hormone is concerned. Slow dilatation of the cervix in labour, therefore, can result from (a) uterine inertia, (b) inco-ordinate contractions, and (c) true rigidity of cervical tissue. The latter is a condition in which the rest of the uterus is acting normally, or at least it would act normally if the cervical obstruction were removed. If it occurred in multiparous women it might presumably lead to rupture of the uterus; in primigravidæ, however, it results in disordered uterine action or inertia. When the cervix is dilated or incised easy and often spontaneous delivery is the rule. The clinical features of this condition are backache—referred pain from the cervix, which is intensified during a contraction or when an attempt is made to stretch the cervix open with the examining fingers. Since the difficulty is at the external os the cervix becomes very thin with a sharp, hard, almost cartilaginous edge and is tightly stretched over the presenting part. The latter is often low in the pelvis, having been driven down by good uterine action. Indeed, cases are described in which the head has been pushed through the introitus, still covered by the intact cervix. This is the condition in which spontaneous annular detachment of the cervix is most likely to occur. Provided the cervix is thin and the presenting part low the appropriate treatment is cervicotomy. When the cervix, and possibly the lower segment too, resists dilatation a not uncommon finding is that the external os becomes displaced, usually upwards and backwards behind the presenting part. This could be accounted for on the assumption that there is unequal and irregular softening and stretching of the tissues.

One of the practical difficulties is to distinguish a rigid cervix from a resistant lower segment; both might occur together and one might be the cause of the other. Indeed the part played by mechanical soft tissue obstruction in what is collectively called inco-ordinate uterine action is most difficult to assess. The subsequent history of many patients is certainly much more easily explained on a mechanical basis of this kind than on the assumption of a purely functional upset in a neuromuscular mechanism which might be expected to recur or to arise in pregnancies other than the first. One line of inquiry which promises some hope in the elucidation and successful treatment of some of these most difficult cases of prolonged labour is to determine the factors which are responsible for converting the rigid non-pregnant cervix into the soft and distensible structure which is normally present in late pregnancy and labour.

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## DISCUSSION

*Dr Sturrock* said that obstetrical judgment between the often conflicting interests of mother and child was nowhere so difficult as in inco-ordinate action of the uterus. He believed that there were three differential diagnoses to be considered in cases presenting this symptom-complex. Was the patient



actually in labour? If in labour, was she suffering from inefficiency of the uterus, or was the condition that of uterine colic? The diagnosis was not easy, but must be attempted if rational treatment were to be employed. A history of rupture of the membranes did not clarify the doubt and very careful analysis of all factors was necessary in all cases showing failure to progress when labour appeared to have lasted some thirty hours. In ætiology, he considered minor disproportion to be important, both that form of disproportion due to a large child with a pelvis at the lower limit of normality, and also the relative disproportion associated with occipito-posterior position or undoing of the flexion of the foetal head. In management, the liberal use of morphia with hyoscine was justifiable, but certain physical measures might also be helpful. For example, if the membranes were unruptured, their digital detachment from the lower segment of the uterus might be followed by improved contractions, while pressure made over the sinciput if maintained during a contraction of the uterus during vaginal examination might encourage a return of an extended head to full flexion, with beneficial effect. He referred to that form of disordered uterine action, to be distinguished from inertia due to exhaustion of the mother, which showed itself in the second stage by gradual failure of the pains eventually necessitating a difficult forceps operation. The victims of this condition were usually in good condition and often required large quantities of general anæsthetic for delivery. Here again a minor degree of disproportion or the resistance offered by the soft tissues were underlying factors in ætiology.

*Dr Haultain* said he felt that Professor Jeffcoate's figures had indicated a rather higher incidence of disordered uterine action in private patients than in hospital patients. *Dr Haultain's* impression was similar. He felt that this condition might be described as occurring chiefly in more sophisticated communities, and felt this was possibly also applicable to the dystrophia dystocia syndrome; might the cause not be anthropological in many cases, rather than endocrinal or nervous? He agreed that minor disproportion was of ætiological importance.

*Professor R. J. Kellar* said he had experience of a case of eclampsia in which a very tight constriction ring developed during treatment by large parenteral doses of magnesium sulphate. Incidentally, as might have been anticipated, this aspsasm was unaffected by curare. He enquired whether Professor Jeffcoate had observed any alarming fall in blood pressure following the administration of tetra-ethyl-ammonium-chloride, and whether he had been able to carry out quantitative estimations of oestrogen in cases of disordered uterine action.

*Dr Hector MacLennan* said he had been impressed by Professor Jeffcoate's analysis of the subsequent labour and mode of delivery in patients who had suffered from inco-ordinate uterine action in previous pregnancies. It seemed, from his analysis, that where the patient's labour had previously been terminated by cæsarean section, the subsequent results were less favourable than when the labour had terminated by vaginal delivery. He therefore wished to make a plea that wherever possible patients should be delivered by the vaginal route, and, when the head entered the pelvic cavity, there was still a definite place in skilled hands for manual dilatation of the cervix followed by forceps delivery.

*Dr C. D. Kennedy* said he had little doubt that the main cause of disordered uterine action was fear. He felt that there was a field for the use of oxytocics in the atonic group of cases, but that with hypertonics these drugs were contraindicated. The differential diagnosis of these two forms was not easy, and the development of a convenient method of recording uterine tone and

contraction was urgent. A suitable tocograph would be a most useful instrument.

*Dr T. M. Abbas* said in a recent investigation in external hysterography he had had the opportunity of observing two cases of uterine inertia both of which had shown hypertonus. He felt that careful recording by the tocograph should be employed on these cases, particularly with a view to studying the precise events which occurred when the ineffectual uterine action gave place to a satisfactory contraction, as happened in the majority of cases.

*Dr J. A. Chalmers* said it was interesting to correlate Professor Jeffcoate's observations in respect of rectal spasm with the well-known favourable results of emptying the bladder and bowel in cases of inertia. He discussed the importance of delayed formation of the lower segment as a cause alike of the high head in the last weeks of first pregnancy and also of the disordered action of the uterus which commonly supervened in such cases. He enquired whether incisions of the cervix were ever followed by dystocia in a later labour.

*Dr A. S. Duncan* said he still believed that fear was an important factor in the causation of inertia. He did not consider that the infrequent recurrence of inertia was a very convincing argument against this. He thought the fear of the unknown was the chief terror of first pregnancy, and that, no matter how grave the suffering of a patient in her first pregnancy, the mere fact that she had survived the ordeal made the patient's dread less in a later pregnancy. He emphasised that the fear was not infrequently entirely subconscious. A psychiatrist might uncover such fears which had escaped less skilled investigators.

*Dr W. I. C. Morris* said he shared the general clinical impression that minor disproportion was common in cases of uterine inertia, but found it difficult to correlate this with the fact that so many neglected cases of gross disproportion showed very good uterine activity. It seemed reasonable therefore to infer that disproportion could not be a very important cause of inco-ordinate uterine action. Did Professor Jeffcoate agree with the common clinical impression that disordered action of the uterus in the first and second stages was commonly followed by similar behaviour in the third stage? If so, did he favour elective manual removal of the placenta following operative delivery in such cases?

*The President* noted that Professor Jeffcoate considered that easy dilatation of the cervix would occur in a second labour following one terminated by cæsarean section for inertia when the cervix was half or more dilated. With this statement he was in full agreement, but the converse was not true. An easy labour could follow a cæsarean delivery carried out for inco-ordinate action when the cervix was only one or two fingers dilated. The President had carried out manual dilatation of the cervix and cervical incision on a number of occasions when the head was deep in the pelvis and the cervix well thinned-out. He was satisfied that these measures were sometimes preferable to section, especially as a living or undamaged child could not be guaranteed by abdominal delivery. A classical section might be preferable in the circumstances in some instances rather than the lower segment operation, now that antibiotics were available. Elective cæsarean section was very seldom, if ever, indicated for a history of previous inertia. Professor Jeffcoate had not over-emphasised the factor of fear. It was undeniable that many patients were so affected; but, on the other hand, true inertia might occur in young women who exulted in their prospective motherhood and began labour without any evidence whatever of fear or undue apprehension. It was abundantly evident that the high head in a primigravida at term could

be due solely to an unrelaxed lower segment, and the small head was frequently held high for this reason. Induction in these circumstances sometimes resulted in inco-ordinate uterine action, while the later onset of spontaneous labour was usually followed by a smooth progress.

Early manual removal of the placenta as an elective procedure following instrumental delivery for inertia was sound practice, if ergometrine did not immediately separate the placenta. The President had advocated this procedure for a long time as the result of clinical experience, for the behaviour of the uterus in the third stage of labour was unpredictable in these cases. He was glad to hear Professor Jeffcoate emphasise the different clinical types of faulty uterine action for the term "inertia" could be grossly misleading.

*Professor Jeffcoate*, in reply, said he did not agree that the fear was less in a second confinement than in a first in the type of case which he had described. In cases given tetra-ethyl-ammonium chloride the blood pressure had rarely fallen by more than 20 mm. mercury, and dangerous side-effects had not occurred although minor disturbances of vision, and dizziness were the rule. He had no experience of oestrogen assays in his patients. He agreed that third stage complications frequently followed operative delivery in these patients, but was cautious in attributing these to persistence of the disordered uterine action, since other factors tended to operate at the time of completion of the second stage. For example, a general anæsthetic was usually given, and often the anæsthesia was necessarily deep, as a result of which uterine activity might be profoundly diminished. He agreed, however, that early manual removal of the placenta was often prudent. He had a strong impression that inco-ordinate action of the uterus was more common in private than in hospital patients, but the accumulation of reliable figures was difficult. There were similar difficulties in regard to assessing the accuracy of antenatal prognosis in respect of disordered action of the uterus. He believed the finding of a high head before labour might well in itself be evidence of a resistant lower segment. He agreed that it was sometimes difficult to be sure when a patient was or was not in labour, and sometimes mistakes could have tragic consequences. It had been suggested that gross disproportion was not characteristically associated with disordered uterine action. This statement required critical examination. It was noteworthy that rupture of the uterus was rare in the primigravid patient. He believed this was attributable to the fact that in the presence of obstruction the primigravid uterus responded by hypertonus with diminishing activity, in contradistinction from the parous organ which reacted with vigorous contraction. These phenomena were supported by tocographic studies, which did appear to indicate that disproportion was an important ætiological factor. He disliked the term "inertia" except when reserved for the atonic form of disordered action. Its use tended to perpetuate the use of oxytocics in treatment, which might have serious consequences in the hypertonic form. He thought it would not be profitable to compare a large series of cases treated by cæsarean section with a similar series treated by cervical incision and forceps. These treatments were not always reasonable alternatives, the case suitable for cervical incision being not necessarily the same as the one suitable for cæsarean section and vice versa. He considered cervical incision should be reserved for those cases where the head was deep in the pelvis and held up by a thinned-out cervix closely applied to it. He was convinced that the condition of "rigid cervix" was a very real clinical entity, though its ætiology was not yet clarified.

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# Edinburgh Medical Journal

May 1949

## INAUGURAL LECTURE

By PROFESSOR WALTER MERCER

THE establishment of a Chair of Orthopædic Surgery in this University is an event in the history of surgery, and more especially of orthopædic surgery, in Scotland. This, the only Chair of Orthopædic Surgery in Scotland, owes its inception to the public-spirited and imaginative benevolence of the late Mr George Harrison Law. A son of one of the pioneers of *The Scotsman*, and, like his father, one of the proprietors of *The Scotsman Publications* for many years, his interest in orthopædic surgery was stimulated by his friendship with Sir Harold Stiles, through whom he met Sir Robert Jones, the great orthopædic surgeon. Mr Law was always keenly interested in and sympathetic to cripple children, and it is said that he seldom passed a little cripple in the streets without stopping for a kindly word with him. This warm interest was fostered by his friendship with Professor Alexis Thomson, and it was through him that he first offered anonymously a sum of money which enabled the University to establish a Lectureship in Orthopædic Surgery, and later to found this Chair.

It is significant, too, that Mr Law's sister, the late Mrs Mackinnon, who died so recently, was at one time President of the Children's Hospital in Melbourne, and organised and opened a hospital in that town much on the lines of the Princess Margaret Rose Hospital in Edinburgh.

I had the privilege of knowing Mr Law, and knew him to be a man of great modesty, who wished no personal credit for any of his kindly actions, and least of all for his gift to the University which made this Chair possible. It was sufficient for him to know that he was doing something that promised betterment for the lame and the halt.

Possibly it was his own keen interest in all forms of sport that gave him his deep sympathy for those whose activities were restricted, for he himself loved to play a salmon on the Helmsdale, to stalk in his deer forest in Sutherland, or to play a round of golf especially in former days, with his friend, the great Freddie Tait. I value the opportunity of paying tribute to this warm-hearted gentleman.

From the earliest days orthopædic surgery has been included in the province of the general surgeon, and so the development of the specialty of orthopædics can be traced through the history of surgery as a whole. It is only since the First World War that we have seen the evolution of the specialist orthopædic surgeon in this country,

and undoubtedly the stimulus of war was an important influence in this direction.

Orthopædic surgery is the modern interpretation of the word "orthopædia," which was first used in the monograph published in 1741 by Nicolas André, Professor of Medicine in the University of Paris. He formed it of two Greek words—"orthos," which signifies "straight, free from deformity"; and "paedios"—"a child," to express his belief in the theory that many of the deformities of adolescence and adult life originate in childhood. He said "Out of these two words I have compounded that of 'orthopædia,' to express in one term the design I propose, which is to teach the different methods of preventing and correcting the deformities of children." The scope of orthopædic surgery, however, has outgrown the limitation originally proposed by André, who confined his thesis to the prevention of crookedness in children.

The history of surgery in Scotland, and of orthopædic surgery, has been greatly influenced by the varying conditions of the country during the last few centuries. It may be interesting, therefore, to consider for a moment the beginnings of a regular system for the care of the sick and hurt, and to recall some of the great men of the past whose labours, often in difficult circumstances and unsettled times, have laid the foundations of this branch of surgery as we know it to-day. In the earlier centuries the healing art had been in a most primitive state; its knowledge the most meagre; its practice the most crude; its methods the most empirical.

The conditions in Scotland during the Renaissance and the seventeenth century were not such as to encourage the development of surgery. About 1600 the entire population of Scotland was possibly about 250,000, and it may have been much less. The population of Edinburgh at that time has been estimated as 9000, and of Glasgow as about half that number. Our forefathers of these days were not town dwellers; they lived in scattered and scantily populated villages and forced a bare livelihood from the soil.

The times were terrible in this century, and in Greyfriars Churchyard the Covenanters signed the Solemn League and Covenant with their blood, and men by thousands died for the faith that was in them. The great Marquis of Montrose was hanged and quartered at the Market Cross. After the Union of 1707 the city grew, but men still were fretful. Mob law prevailed and Captain Porteous of the City Guard was hurried to the Grassmarket and hanged from a pole. These Edinburgh mobs were said to be the fiercest fighters in Europe. Bonnie Prince Charlie held his Court in Holyrood in 1745, and with the last of the Stuarts, law and order began to assert itself. It was in such times and in such a cradle, in a Scotland convalescent from a century of blood, that orthopædic surgery was born.

The most important step towards reforming surgery and founding a Medical School was taken in 1720 with the appointment of Alexander

Monro, better known as Monro primus, at the age of 22 as Professor of Anatomy in Edinburgh at the princely salary of £15 per annum. Under his brilliant teaching, and fired by his enthusiasm, his class, at first numbering 57, rose to 400, and soon from England and Ireland young men were attracted who had hitherto thronged to Holland.

Other professors and teachers were appointed at the same time and there was formed a Medical School which was to achieve a European reputation for the University, and to change a craft into an art, and empiricism into the semblance of a science. It was Monro primus who, in 1738, made Edinburgh's first notable contribution to orthopædic surgery.

During this century interest in orthopædic problems was widespread. In every medical community individuals were devoting their energies particularly to the treatment of spinal deformities and knee conditions. Most disabilities involving the knee joint were considered by both the profession and the laity to be exclusively within the domain of the unqualified bone-setter. To use the parlance of the day, the "joint was out," and the treatment by the bone-setter ostensibly resolved itself into throwing it back into its proper relationship.

Although loose bodies in the knee had been noted by Paré in the sixteenth century, the first real description of them and of their origin from the cartilage of the articulating surfaces of the knee was given, appropriately enough, by an anatomist—this famous Alexander Monro. Monro primus was born in 1697 and as a young man he was sent to London to study under the famous Cheselden, and later to visit the Medical School in Paris, and to work with the great Boerhaave at Leyden.

He later published his *Anatomy of the Human Bones*, which went through eight editions in his lifetime, the later ones including a "Treatise on the Nerves." It was translated into most European languages and earned a reputation for Monro which did much to increase the fame of the new Faculty of Medicine in Edinburgh. Some of the anatomical dissections made by Monro, and presented to the College, are still to be seen in our Museum. Monro and Lord Provost Drummond are rightly considered the Founders of the Royal Infirmary of Edinburgh. An interesting tribute to Monro comes from the pen of Oliver Goldsmith, perhaps his most famous pupil, in which, in the conclusion of a letter to his uncle he says: "You see then, dear Sir, that Monro is the only great man among them, so that I intend to hear him another winter and go then to hear Albinus, the great professor of Leyden."

Monro gave up lecturing in 1759 and confined himself to giving clinical instruction with Drs Cullen and Whytt, both of whom deserve mention in these remarks, for Cullen, a pupil of Monro, and a holder in his lifetime of Chairs both in Glasgow and Edinburgh, was the first in the country to give clinical lectures in an infirmary, and the first ever to lecture in the vernacular instead of in Latin.



Robert Whytt had by this time become a bright luminary in the rising University and, as one of the most brilliant of the early Edinburgh professors, left his mark on physiological science. He was appointed Professor of the Theory of Medicine in this University in 1747, and four years later published his book, *An Essay on the Vital and other Involuntary Movements of Animals*, which attracted the attention of physiologists throughout Europe.

Whytt made the important discovery that distinct segments of the spinal cord controlled the reflex arcs of specific areas, and that the continuity of the entire cord was not essential to the reflex action of any given muscle group. He was thus the first to localise the seat of reflex action in the spinal cord and to show that it was independent of the brain. Whytt's chief claim to lasting remembrance, however, lies in the fact that he was the first to give a clear description of tuberculous meningitis or, as he called it, "Dropsy of the Brain." In a short article of 23 pages he described this disease according to three stages, and even at the present day there is little to add to his description from the clinical aspect.

About this time public service of a high character was rendered by Sir John Pringle, who is regarded as the founder of modern military surgery. He was born in Stichill, Roxburghshire, and studied in Edinburgh and Leyden. After graduating at the latter University in 1730, he returned to settle in Edinburgh. His settling, however, must have been disturbed, for though appointed Professor of Moral Philosophy and combining this with the practice of surgery—in both of which he was eminent—he acted as surgeon to the armies on the continent in the mid-century wars. It was about the time of the Battle of Dettingen (1743) that he made the historic suggestion to the Earl of Stair, to whom he acted as military surgeon, that the military hospitals of both the French and the English sides should be regarded as neutral and immune from attack, and so made the first suggestion that led eventually to the formation of the Red Cross Society. Pringle says: "But the Earl of Stair, my late illustrious patron . . . proposed to the Duke of Noailles, of whose humanity he was well assured, that the hospitals on both sides should be considered as sanctuaries for the sick, and be mutually protected. This was readily agreed to by the French General, who took the first opportunity to show a particular regard for his agreement. . . . This agreement was strictly observed on both sides all that campaign, and although it has been since neglected, yet we may hope that on future occasions the contending parties will make it a precedent."

This arrangement, which was rigidly observed, remained in force and led eventually to the Red Cross Organisation in warfare being put on an absolute basis through the efforts of Henri Dunant, a Swiss banker, in the Geneva Convention 121 years later.

Pringle was a pioneer of the antiseptic idea, and in his paper "Experiments upon Septic and Antiseptic Substances," read before

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The great work on surgical anatomy of John Bell (1765-1820) exerted a powerful influence upon the surgery of his time, and he was, with Desault and John Hunter, a founder of the modern surgery of the vascular system. He himself had tied the common carotid artery and the internal iliac and was, indeed, the first to ligate the gluteal artery.

After spending some time amongst the wounded men of Lord Duncan's Fleet after the battle of Camperdown, he wrote his treatise on "Gunshot Wounds," which contains evidences of much careful observation and sound deduction. We in our day have had to re-learn much that was known to John Bell and had been forgotten. Bell deserves credit for his investigation into the doctrine of inosculating arteries, whereby many limbs were saved from amputation. He believed that those vessels were sufficient to maintain the blood supply, even though the main vessel was ligated very proximally. He further advised the approximation of wound surfaces so closely and evenly in contact that they might adhere to each other. This was quite the reverse of the usual procedure, where the skin and deeper layers were dressed as separate sores till the twelfth day with, as Bell says, a rudeness and ignorance quite unparalleled, and so he was the first to attempt to obtain the primary union that is the usual achievement to-day.

The credit of initiating this advance in surgical practice cannot be allocated to any single person, but John Bell's work on inosculating arteries contributed to give it a rational basis.

Bell described an early but unsuccessful experiment in what would now be called aneurysmorrhaphy, where he opened an aneurysm, hooked out the clot, and stitched the opening in the main vessel. The operation was apparently successful, but the patient had a hæmorrhage, no doubt from sepsis, on the twelfth day and died. He believed, as so many of us do to-day, that operations usurp an undue importance in medical education. "Operations," he said, "have come at last to represent, as it were, the whole science, and the surgeon, far from being valued according to his sense, abilities, and general knowledge, is esteemed excellent only in proportion as he operates with skill." How right he was in his objections to this attitude, and how modern, is proved by the orthopædic outlook to-day.

The first incumbent of the Chair of Surgery in this University, founded in 1803 by George III, was James Russell (1755-1836) who was already the President of the College. We owe to him some important contributions in orthopædic surgery. It is a curious fact that when he was appointed to the Chair he ceased to be a practising surgeon at the Infirmary. Having thus no beds, he wandered about at his own sweet will, and lectured on the cases of the other surgeons. The position must have been a delicate one since criticism would cause trouble and mistakes would have to be ignored. Although Russell is stated to have skated successfully over this thin ice, it is

not surprising that a contemporary writer tells us that while Russell lectured on the cases of the other surgeons, making remarks on their treatment, they, especially Mr Liston, made remarks on him.

Russell, at the age of 39, wrote a practical essay on a certain disease of bones termed "necrosis"—what we now call osteomyelitis—and this constitutes the first attempt to give a complete and detailed description of a common surgical affection of the time. It has the merit of being original, but it brings out the fact that though the condition was known to Albukasim, who flourished in Arabia in the eleventh century, it was not till 600 years later that Scultetus described a typical case, and that even such modern surgeons of the time as Hunter, Gooch, and Cheselden were but imperfectly acquainted with the nature and course of the disease. This essay is of value chiefly for the full and systematic description he gives of the clinical course of the disease. In his treatment he unconsciously gropes towards the modern doctrine of artificial hyperæmia in suggesting warm fomentations in the early stages.

A contemporary writer in the *Medical Times and Gazette*, describes Russell as a tall, thin gentleman, who wore a red wig, and was always dressed in black, with a white neck-cloth—not a tie, but a "choker" of the Beau Brummel type. He indulged in a broad frill on his shirt, and knee breeches, though the muscular development of his lower limbs hardly warranted this attire. He is said to have yawned while he lectured, and continued to lecture while he yawned.

This University can lay claim to a share of the glory reflected from the name of Sir Charles Bell (1774-1842), for it was in this city that his attention was first turned to a study of the nerves. He was the son of an episcopalian minister of Doune, Perthshire, and a brother of John Bell, in whose anatomical room he acted as assistant.

His brother, John, was deeply involved in medical polemics, and, lest the prejudice aroused should be extended to himself, Charles decided to remove to London, taking with him the manuscript of his first great work on the *Anatomy of Expression* which at once established his reputation. Through his ardent devotion to private investigation he never acquired the practice he had hoped for in London, and eventually accepted the Chair of Surgery in Edinburgh. His researches on the function of the nerves culminated in his great discovery that there were two kinds of nerves—"sensory" and "motor"—each subserving its own purpose. In 1807 he wrote to his brother, George, later Professor of Scots Law, of his new ideas and of how he had noted that when he pricked the posterior filaments of the nerves no motion followed, but that when he touched the anterior filaments the parts were immediately convulsed. Thus was the function of the spinal nerve roots demonstrated, though the conclusive experimental proof was left to Magendi twelve years later because Bell so disliked animal experimentation. In addition to proving that there are two great classes of nerves, he discovered many other important facts

regarding the function of individual nerves. He demonstrated that the fifth cranial nerve is a mixed nerve, and described Bell's paralysis of this nerve, as well as the paralysis affecting the scapula, resulting from a lesion of the external respiratory nerve of Bell. On his return to Edinburgh, he filled the Chair with acceptance, published a book on surgery, and revised his work on the nervous system, while his *Bridgewater treatise* on the hand had a great vogue and passed through many editions.

Bell was a genial, unaffected, kind-hearted man, with a captivating twinkle behind his eyeglasses, and with something of the dandy in his attire. He was much lionised in London, and in 1829 was knighted for his physiological discoveries. He was an able surgeon and attended the wounded after the battles of Corunna and Waterloo, making interesting sketches of what he saw.

The surgical school of Edinburgh was now, in this, the first half of the nineteenth century, at the height of its fame, but two figures stood out above all the others, and to both orthopædic surgery owes a debt.

Robert Liston was a son of the manse and was born at Ecclesmachan in Linlithgowshire. He became a student of John Barclay, a great anatomist, in 1810, with the ambition of becoming an operating surgeon. Later he had anatomy rooms of his own and with the help of James Syme as demonstrator he taught a class of sixty students. Many tales are told of his escapades as a resurrectionist in those days when anatomical material was scarce. He might well, says Guthrie, have been the original Dr McFarland of Robert Louis Stevenson's *The Body Snatcher*.

Syme and Liston were at first great friends, but the constant association of two such brilliant men inevitably led to difference and "a certain coldness between them" ended in an open rupture. Their co-operation and teaching were dissolved and their relations in public were so embittered that Syme was denied the appointment of Surgeon to the Royal Infirmary, as the Managers feared disturbing scenes between them in the presence of students. Liston, however, was defeated by Syme later in a bitter contest for the Chair of Clinical Surgery. This was a crowning blow and influenced Liston in accepting the offer of the Chair of Surgery at University College, London, but, though depriving the surgical school of Edinburgh of one of its brightest ornaments, his time in London was so fully occupied that he wrote little of importance after leaving Edinburgh.

One of Liston's earliest and most notable contributions to orthopædic literature was on "Fractured Neck of the Femur." In this he pointed out the absolute necessity of replacing the fragments and of securing their immobilisation, and in it he disagreed with the views of Sir Astley Cooper, especially on the effect of synovial fluid on the union of the fracture. He proved that there is no reason why a fracture of the neck of the femur should not unite as well as any other when put in circumstances favourable to such an occurrence. That his views were

sound is proved by the fact that his statements are acceptable to us to-day.

His methods were hardly up to the standard of his theories, but they are at any rate in use to-day, though only occasionally and then as first-aid measures, for he introduced what we now know as Liston's Long Splint. He introduced many novelties, such as the flap method of amputating, the credit for which is granted to him even by modern American literature; his shoe for club-foot; and his devices for reducing dislocations. He described, in his chapter on "Tendons" in his *Practical Surgery*, an ingenious apparatus for the treatment of ruptured tendo-Achilles, and points out that Monro primus and John Hunter both suffered this accident. Dr Guthrie describes in his *Travel Journal of Peter Camper* how the accident to Monro happened while the victim was dancing the Scottish reel.

Liston in his book says of this ruptured tendon—"It is an accident that most frequently occurs to those who have been for a time unaccustomed to violent action of the muscles. It happens to gentlemen of mature years, who, forgetting these, join in the sports of youth, attempting to skip and dance as they were wont to do; suddenly they suppose that someone has inflicted a blow on the leg from behind—their dancing is arrested, the foot cannot be extended, and the nature of the case is forthwith apparent to the most careless observer." How much more graphic than the stilted descriptions in textbooks of to-day! Liston published a remarkable series of cases of aneurisms, five in number, which had occurred in his own practice over a period of five to six weeks, and in this paper he recorded the first successful case in Britain of removal of the scapula without sacrificing the arm—an entirely original procedure—as well as the first successful case of ligation of the subclavian artery. He is still remembered, too, for what he then called his "Bone pliers." These were made for him by "Mr Young, a most ingenious cutler in College Street," and were designed to deal with metacarpals. They were soon found, however, to have a much wider application, and to this day Liston's Bone Forceps are found on every instrument table.

Liston was often rough, abrupt and contentious in public relations, but was kind and charitable to the poor, and gentle in the sick room. He is described as wearing a bottle-green coat with velvet collar; double-breasted shawl vest; grey trousers, and Wellington boots: the thumb of one hand stuck in the armhole of his vest; and chewing an orange-stick tooth-pick. With one or two exclusions from this description—notably the coat and the tooth-pick—he can be seen in a painting now in University College, carrying out the first operation under ether in this country—an amputation—a bare two months after Morton's successful demonstration in the Ether Dome in Massachusetts General Hospital in October 1846. One of those who witnessed Liston's operation, and who can be seen in the painting, was Joseph Lister, then a student.

James Syme, who has been called the Napoleon of Surgery, was born in 1799 in his father's house in Princes Street, almost opposite where the Scott Monument now stands. Shy and reserved as a boy, he made few friends among his High School fellows, and shared little in their outdoor sports. When studying chemistry at the age of 16 he discovered a solvent for rubber and found that by brushing the solution on a silk coat he rendered it waterproof. His publication of this was noted, and a Glasgow manufacturer, Mackintosh, adopted the invention and patented it, and, making a fortune from it, secured an adventitious immortality for his name.

Syme was a cousin of Liston, and commenced his career by teaching anatomy and practising surgery along with him. The quarrel with Liston and his failure to secure an appointment in the Royal Infirmary left him undaunted, and, as all that he wanted was a hospital, he established one of his own. He leased Minto House, a town house of the Elliots of Minto, and converted it into a private hospital—perhaps the earliest private nursing home in Edinburgh. There he developed the innovations and improvements with which his name is still associated.

Syme's most important contributions to surgery were on amputations and excisions. In the early part of his career, when he was forcing his way up the Edinburgh surgical ladder, a woman of 38, Christina Lawrie, came to him with caries of the shoulder joint. He decided to resect the joint and try to save the limb, and this operation was successful. In his *Excision of Diseased Joints*, published in 1831, he was the first to show that excision is usually preferable to amputation, and the adoption of this new principle is due to him, although it was afterwards more fully developed by Ferguson. At this time resection of a major joint was a formidable undertaking, carried out only occasionally by a very few of the exceptionally daring surgeons. Syme's impressive plea for excision as an alternative to amputation was a lasting contribution to conservative surgery. If he had done nothing else he would have been one of the great benefactors of the human race.

In 1835 he had to treat the case of a young girl who suffered from osteomyelitis of the tibia. After performing an amputation he dissected the leg and found new sheets of bone covering the dead shaft which were apparently produced by the periosteum. To determine that periosteum could and did produce bone, he carried out an interesting series of bone experiments on dogs and convinced himself that this was so.

Amputations of the foot were devised about this time by Lisfranc, Pirogoff and Syme, of which the most interesting, and the only one now in use, is the last. It has had a varied career, and had fallen from grace before the last World War, due to a great extent to the influence of limb-makers who, from their point of view, favoured a higher amputation. Its chief advantage is that it not only leaves the leg but also a stump on which the whole weight can be borne unaided

by any artificial limb. Although Edinburgh surgeons have always championed this operation, its most powerful advocates came from Canada. In 1941, Gallie, after studying the amputees over a period of twenty years, recommended the Syme operation for all cases suitable for a low amputation. The United States Army and Navy Hospitals also continue to favour the method, and in 1946 Thomson and Aldridge published a very favourable report on it from the Army Amputation Centre. It has been said that on this achievement alone Mr Syme might have based his reputation as one of the greatest surgeons who ever lived.

Syme was the first in this country to perform the operation of subcutaneous tenotomy for wry-neck, and excision of the clavicle for sarcoma. He was a dominating figure in European surgery for a quarter of a century. There were "few advances in surgery that had not received some impulse from his indefatigable and vigorous mind."

Fortunately his quarrel with Liston ended happily, for Liston wrote to him saying he could not resist the temptation of saying a few words with a view to bringing about a reconciliation. "Write and tell me that you wish to have our grievances and sores not plastered up but fairly cicatrized." Syme was equally generous, and the old friendship was renewed and later, when Liston visited Edinburgh, he spent much of his time under Syme's roof at Millbank, a house now incorporated in the Astley Ainslie Hospital.

Syme was a genial, happy, even-tempered man, though with controversial tendencies. He is said never to have wasted a word, nor a drop of ink, nor a drop of blood. His was a broad-minded liberal spirit, but he had no patience with shallow minds or superficial thinking.

Sir George Ballingall was appointed Regius Professor of Military Surgery in this University in 1822 and lectured on the subject for thirty-two years. He produced a textbook, *Outlines of Military Surgery*, and it is of interest to us to-day because in it he describes the closed method of healing wounds. He describes how Larrey treated wounds, both simple and compound, with compression and cushions of straw, leaving them undisturbed till the completion of the cure. He points out how the method is akin to that followed by the natives of India, where Ballingall had served for some years. He describes the case of a little native boy who had been run over and sustained a compound leg fracture. He says, "I was preparing to amputate this boy's limb when his parents came and carried him away to the potter in an adjoining village, who enveloped the leg in clay, and I believe finally cured the patient." The method has been re-discovered and Winnet Orr's name and others have been attached to this evidently old method.

John Goodsir was born at Anstruther, in Fife, in 1814. He was tall and gaunt, but in every sense of the term an impressive figure. His features were massive; his eyes were deep-set; his expression was thoughtful, though not infrequently lit up with a glance of humour;



his gait was tottering from an ataxic condition. He always lectured without notes, and in a dress coat, and wore his gown only occasionally. Though hesitating somewhat in speech, and though his accent savoured of his native county, he commanded the attention of his class and aroused their intelligence by his suggestive remarks. "Facts, gentlemen, are what you should aim at; never use the word 'about'; always note the exact amount, measurement or weight as the case may be." In Edinburgh he dressed for Syme, and was fully aware of Syme's researches on the production of bone by periosteum. By the use of the new compound achromatic microscope and the study of marine forms of invertebrate life, dredged from the Firth of Forth, he began to unravel the obscure and complex process of bone building in the human skeleton. He had no doubt that the human skeleton was laid down, not by arteries, but by an element of which Hunter had no conception—separate self-acting units of living matter. He thus convinced himself that living cells acted as depositors and absorbers of bone, not as had been described, the arteries and lymphatics themselves. That discovery marks a new chapter in our knowledge of bone. His investigations were published in 1845 and disagreed, of course, with Syme's conclusions on the same subject. He was of the opinion that periosteum has no bone-forming power. He termed it a limiting membrane and stated that its osteogenic power was inherent in the layer of cells directly beneath it which are almost always removed with it.

Goodsir made important additions to our knowledge of cartilage. Hunter had taught that absorption of tissues was carried on by lymphatic vessels. Goodsir could find no lymphatics in articular cartilage and yet it could undergo absorption. He examined sections of the articular cartilage in a tuberculous joint and noted that the pits in the cartilage—the areas undergoing absorption—were filled with a cellulo-vascular tissue. He satisfied himself that these invading cells were demolishing the cartilage. He observed that as the invaders approached, the cartilage cells multiplied, became large, rounded and swollen, and ultimately ruptured, and their space was then occupied by the invaders. Goodsir traced these invaders to the peri-articular plexus of the joint.

Some years later, Goodsir, this master anatomist of Edinburgh, became interested in the mechanics and the movements of the knee joint, particularly the screwing movement at the joint when it was reaching full extension. Goodsir recognised the screw-home movement as a cunning mechanism for securing and locking the joint. He pointed out that this locking movement becomes impossible if there is the slightest displacement of the semilunar cartilages. He noted and described for the first time the movement of these cartilages in the joint and how they help to fill the inequalities as the joint is flexed and extended and how, when damaged, they impeded the free movement of the joint.

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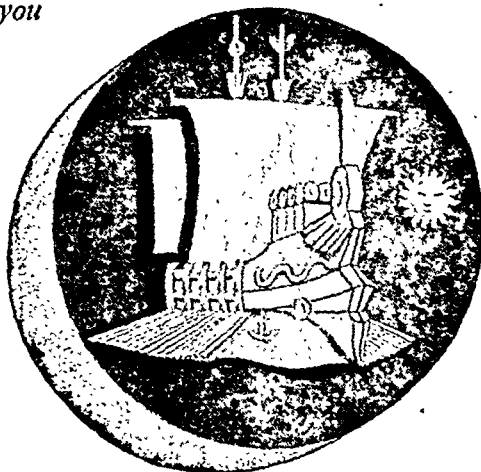
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At about this time Hugh Owen Thomas came to Edinburgh from Wales to study for his Diploma. He arrived with his brother and a letter of a pastoral character. It was written by their minister in Liverpool, and, with old-fashioned decorum, committed them to the care of a worthy citizen of Edinburgh. Hughes Bennett, of Edinburgh, wrote of Thomas at this time as "an honourable and industrious student of an enquiring mind and with a desire to know the truth." So we may assume that his time in Edinburgh, though a short two years, was well spent, and although he gained no academic distinctions he gave evidence of those qualities which proved of such value in later life. He has been called "the father of modern orthopædic surgery," and it is good to think that in Edinburgh he was put on the right road for earning that title. If for no other reason, his name will live for ever because of the Thomas's Splint, which in the first World War reduced the mortality in compound fractures of the femur from 80 per cent. to somewhere in the neighbourhood of 20 per cent.

Goodsir engaged a new demonstrator of anatomy about this time in the person of Thomas Annandale, the son of a surgeon in Newcastle. He became a surgeon to the Royal Infirmary and in 1877 succeeded Lister in the Chair of Clinical Surgery, and in the following years he made history by his operations on the knee joint. The modern practice and acceptance of surgery as a standard procedure in the treatment of affections of this joint began with his work. In 1879 he reported a case of loose cartilaginous bodies recovered from the knee joint by direct incision with antiseptic precautions. From this time on, the surgical removal of "joint mice" became routine in leading centres and numerous case reports appeared, especially from British sources. But even more dramatic was the operation which was recorded in the *British Medical Journal* in 1885 in which he described the first deliberate and planned operation for the relief of the internal derangement of the knee caused by a displaced cartilage. On the 16th November 1883 he opened the joint of—appropriately enough—a miner from the North of England, and found a tear of the anterior horn of the meniscus. The cartilage was drawn forwards, stitched to its proper place, and on 24th January, after seven weeks in plaster of Paris, the patient was discharged cured, the movements of the joint being good and the limb steadily gaining in strength. It is not only the success which attended this, the very first operation on a cartilage, which is of interest, but even more so is the discovery of the exact kind of lesion which caused internal derangement of the knee joint.

There are few professors privileged to hold so high a place in the love and respect of their students as did Tommy Annandale. His was a small, well-made figure, but a conspicuous one. I still remember him. What a privilege I thought it was for me, a first year medical, to be in the same room as this man among men. I won't ever forget his kindly face, his unique brown hospital coat, and his dangling bow tie in pale blue with white spots.

Edinburgh, too, must take some credit for the greatest surgeon, for Lister spent one-third of his active career in this University. He came here at the instigation of two of his London teachers to follow surgery under Syme, whose house surgeon he became and whose eldest daughter he afterwards married. One of his early papers while in Edinburgh was on inflammation and was based on his investigations on the foot of a frog captured at Duddingston Loch. It was the beginning of his investigations which led to his antiseptic theory. It was later, however, that, impressed with the high mortality caused by such surgical pests as septicæmia, erysipelas, and hospital gangrene, he sought for some method of dealing with them and preventing them. And so the whole dramatic story of the discovery of antiseptics became unfolded. On 12th August 1865, he employed carbolic acid in a case of compound fracture, with complete success, and in 1867 he published the results of two years' work in two papers, the second of which bears the significant title—*On the Antiseptic Principle in the Practice of Surgery*. He boldly applied the antiseptic principle to all manner of operations on the locomotor system, doing more to extend the domain of surgery than any man of his time, or, indeed, of any time. Four years later he returned to Edinburgh as Syme's successor and for eight years filled the Regius Chair of Clinical Surgery. During these years in Edinburgh his chief accomplishments were his researches in bacteriology, and his use of the carbolic spray. He planned a new operation for amputation through the condyles of the femur; another one for excision of the wrist joint; experimented with suture material; and introduced the use of buried catgut.

As an operator Lister was not brilliant, but deliberate and careful, aiming always to make the recovery of his patient a certainty. His Quaker sobriety, his severe and austere ideals, were not the traits that make for rapid and showy success. He received during the later years of his life many honours and world-wide recognition. At a Banquet of the Royal Society the American Ambassador, Bayard, addressed him—"My Lord, it is not a profession, it is not a nation, it is humanity itself which, with uncovered head, salutes you." When his body was laid to rest in Westminster the world had buried her greatest surgeon.

Wallace Williamson said of him, in a Memorial Discourse, in St Giles at his death, "Yet greater than his greatest achievement was the man himself, and the final secret of his greatness was that serene simplicity which was his most distinguishing characteristic. His was the grave and thoughtful courtesy which bespoke the Christian gentleman and the earnest lover of his kind."

And so, on this summit of high endeavour and high achievement, I close my story, and it is my earnest hope that the wonderful achievements, often in difficult circumstances, of these great men, may set a target for those whose footsteps I hope it will soon be my privilege to guide.

# A WORKSHOP FOR SEVERELY DISABLED MEN

By T. FERGUSON, M.D., D.Sc., F.R.C.P.E.

## I. THE IDEA OF THE SHELTERED WORKSHOP

THE problem of employment of the severely disabled has long vexed the minds of medical men and social service workers. It is a common problem, though seen perhaps most acutely among orthopædic, neurological and neuro-surgical patients. In a city like Glasgow, still of predominantly heavy industry, the difficulty is often great. Even with careful job-analysis and maximal co-operation by employers, suitable employment for the severely disabled cannot readily be found in the shipyards, docks, and steelworks where most of the patients had previously worked. Apart from lack of suitable jobs, there is the inescapable problem of the immobility of the disabled, and the fact that the patients come from homes widely scattered throughout the city and surrounding district.

Two lines of approach to the problem suggested themselves. Could it be solved reasonably soon by the provision of outwork that could be done by the disabled in their own homes? Or, failing that, would it be possible to set up a sheltered workshop, either within a larger factory, or as a separate entity? On enquiry there seemed to be little prospect of obtaining satisfying work along "outwork" lines for severely disabled persons. Therefore energies were concentrated in an effort to set up in the first instance a workshop to employ some forty disabled persons, with the possibility of subsequent expansion and, perhaps, the provision of outwork for the house-bound, centred on the factory, at a later date.

## 2. THE APPROACH TO THE PROBLEM

Help was sought from the Secretary of the Federation of British Industries in South-west Scotland, indicating the essential conditions for employment of the severely disabled, and asking for advice and guidance from the industrial point of view. After careful study of the problem, the Secretary suggested an approach to the General Manager of Scottish Industrial Estates Ltd., at Hillington, in the belief that the estate might be a suitable setting for a venture of the kind. Hillington is situated just beyond the western boundary of the city of Glasgow, and the estate began to be developed in 1935 as one of the first organised efforts to relieve the Clydeside unemployment of those dark days. It is controlled by a non-profit-making company set up on Treasury grant, though the tenants work under ordinary competitive industrial conditions while availing themselves

A Honyman Gillespie Lecture delivered in the Royal Infirmary, 28th April 1949.

of the services and amenities provided by the estate company at an economic rent.

These were the reasons suggesting that the industrial conditions obtaining at Hillington would be suitable for the purpose :—

- (1) There was great diversity of trade, thus providing a valuable cross-section of industry from which one or more sub-contracts might be secured, as an alternative to the manufacture of an independent product.
- (2) The establishment and maintenance of a sheltered workshop there would be an economic proposition in so far as factory premises could be leased at an economic rent, together with centralised canteen and industrial nursing facilities, thereby eliminating some overhead charges.
- (3) Land was available for further buildings.
- (4) A sheltered workshop established there would operate amidst normal surroundings and conditions, as part of the general industrial activity of the Estate.

The Tenants' Association accepted the principle of a workshop for severely disabled men, and adopted the idea as an appropriate form of war memorial.

It was clear that there was little hope at this juncture (May 1945) of securing a reliable and long-term sub-contract from any tenant on the estate, since already the end-of-the-war industrial disorganisation was causing decline in demand for goods and services of a war-time character, so that large numbers of employees were being paid off from factories on the estate. It was decided to look further afield, and contact was made with Messrs Thermega, Ltd., who had for a number of years been employing, in their factory at Leatherhead, disabled ex-servicemen suffering from neuroses, who were engaged in the manufacture of electrically heated pads and blankets. From this company a sub-contract on favourable terms was secured for an initial period of three years : it is hard to overestimate the value of this sub-contract, for it rendered possible the early opening of the sheltered workshop.

### 3. SETTING UP THE WORKSHOP

It was estimated that some £6000 capital would be needed for the enterprise. The greater part of this sum was subscribed by the tenants on the estate, and on 27th February 1946, a company was incorporated under the name of Haven Products Ltd., as a "private company to provide facilities for persons registered under the Disabled Persons (Employment) Act, 1944, to have employment and to manufacture electro-thermic quilts, etc."

The company's constitution provides that no distribution of profits may be made to its shareholders. Any surplus arising on its activities must be devoted to the objects for which it was formed.

A Medical Advisory Committee was set up, its membership consisting of consultants from the staffs of the three large voluntary hospitals in Glasgow, a Senior Medical Officer of the Ministry of Pensions, three Almoners, and an Observer from the Ministry of Labour. The duties of the Advisory Committee were to advise from the medical angle on the planning and equipment of the factory, to help in the selection of suitable disabled men for the workshop, and to keep in touch with the men at work to ensure that their disabilities were in no way aggravated by working conditions. As an additional safeguard, it was arranged that at the end of each year's service every disabled man would be referred for overhaul to the clinician in whose charge he had been before coming to the workshop, so that his condition could be reviewed, and any necessary treatment instituted, or modification of working activity arranged. The aim throughout has been to keep medical supervision of the workers so far as possible in the background, and to run the enterprise along ordinary industrial lines. But there has been clear recognition of an over-riding responsibility for the welfare of these men and unobtrusive machinery for safeguarding their health.

Since it was contemplated that a number of paralysed men would be employed at the Hillington factory, negotiations were opened with the manufacturers for the production of machines with controls that would lend themselves to adaptation to individual requirements. Benches were constructed to a design which would allow a chair-bound worker to manœuvre into a comfortable working position, and the lay-out of the benches was arranged to allow free access to and from these positions. Doors were specified of a width to allow the passage of invalid chairs. Rest-room facilities were provided, and arrangements made to install heating equipment well in excess of statutory requirements. Special attention was paid to the provision of suitable lavatory accommodation for chair-bound employees, and supporting rails were conveniently placed with overhead trapeze to enable a chair-bound patient to make full use of his arms.

Ample lighting was provided, and the workshop was brightly decorated, yellow and green being chosen as the colour scheme. Canteen facilities were available on the estate within a short distance of the factory, and arrangements were made for the disabled men to be given service at a cafeteria on the ground floor.

The demands of the several jobs in the manufacturing process were analysed and a schedule showing the requirements for each prepared for the information of the panels of the Medical Advisory Committee which were to be responsible for selecting the employees. Most of the men are employed in machining, element-wiring, or flex-fitting—all sedentary jobs. Machining involves the operation of power-driven sewing machines, using controls modified to suit individual disabilities; threading of needles, changing of spools, etc., calls for full use of the hands. Element-wiring lends itself to the employment



of the most severely disabled ; it entails threading element wire back and forward across a table from one worker to another through 20 "pockets" of the blanket, using a 3-foot threading rod for the purpose. Flex-fitting requires the normal use of both hands and involves simple light soldering.

The workshop was opened on 25th March 1946 with two foremen, one storekeeper and the manager. One week later, on 1st April, 14 more disabled men commenced training, the policy being to build up the labour force slowly, concentrating on quality production and reducing wastage to an absolute minimum. This policy of building up slowly to an optimum labour force allowed the most advantageous placing of individuals from medical and production points of view.

The Ministry of Labour agreed to pay training allowances for twenty-six weeks' training for each disabled person. These training allowances were at the following weekly rates :—

Single man . . . . .	£2 5 0
Marriage allowance . . . . .	0 10 0
First child . . . . .	0 4 0
Allowance for meals . . . . .	0 5 0
Travelling allowance according to scale.	

At first a basic wage of 2s. per hour was paid on completion of training, with usual statutory holiday payments ; and in addition a bonus, paid at mid-summer and the end of the year, which in the first year averaged £8 per man. Later it was found possible to raise the basic wage to 2s. 1½d. per hour. Consideration was given to the possibility of paying a collective production bonus, but it was decided not to do this, partly because of a fear that such a bonus would inevitably accentuate the difference between the more able workers and the others and so might imperil team spirit, and partly because of a fear that a bonus of this type might tend to overstrain workers already handicapped.

In view of the determination to make ends meet, it was considered necessary to have a working week of forty hours. A five-day working week was adopted, with hours of work from 8.30 a.m. to 12.15 p.m. and from 1.15 p.m. to 5.30 p.m. : breaks of fifteen minutes were made for tea at 10 a.m. and 3 p.m. During the six months' training period allowances were paid during sickness absence up to a maximum of three weeks, but subsequent to training no payment was made for absent time.

#### 4. RECRUITING THE WORKERS

When the time came to recruit workers for the factory, the city hospitals, Erskine Hospital, the Ministries concerned, and the Cripples' League, were invited to submit to the Medical Advisory Committee the names of seriously disabled men whom they considered likely to be suitable candidates for employment.

Many names of potential workers were received by the Medical Advisory Committee, far more than the workshop could accommodate.

Information about the industrial history and social circumstances of each applicant was obtained, together with a full medical report, and an analysis of the patient's residual disability. In making a preliminary selection certain broad factors were kept in mind. First in importance was the range of work which the applicant could hope to overtake, relative to the kinds of work available in the workshop. On the one hand it was necessary to insist on capacity to do some useful work—a reasonable prospect of being able to do at least moderately well one of the several jobs into which the work of the factory fell. On the other hand there had to be kept in view the primary function of the workshop—that it was essentially a place for the employment of men with disabilities so severe that they had little or no prospect of obtaining or holding work under ordinary industrial conditions. The only minor exception to this policy arose from recognition that it would be necessary, in the interests of production, to employ a few men, perhaps up to 20 per cent. of the total, whose disabilities might be rather less severe than the general level—men, for example, who would be able to provide the degree of mobility and relative fitness required in one or two key jobs, and to meet this need a few men were accepted whose disabilities were not as serious as the others.

So far as possible, due weight was given to relevant social considerations, for it was the aim to use the limited number of places available in such a way as to afford the greatest possible amount of social service.

Then there was the question of place of residence in relation to the workshop. Housing is the corner stone of any scheme for the welfare of the severely disabled. It was realised from the start that every effort should be made to secure suitable houses in proximity to the factory. The provision of a small housing estate was beyond the financial scope of the tenants, but the Scottish Branch of the British Red Cross Society generously undertook to contribute money to cover the provision of 20 houses for ex-servicemen. The intention is that these houses will be provided through the Scottish Veterans' Garden City Association, and it is hoped that it will be possible to arrange similar accommodation for the civilian disabled employed in the workshop, though it is realised that this raises formidable administrative difficulties.

Some of the applicants for employment, and among them the men whom the workshop could do most to help, were quite incapable of travelling to work by any form of public service. A few had motor chairs, but there remained many for whom the possibility of workshop employment was completely bound up with the possibility of organising special transport service. The homes of these men were widely scattered through the city, but by arrangement with St Andrew's Ambulance Association, who undertook to provide a service at greatly modified cost, it was found possible to arrange routes that would

permit the transport of a number of disabled men who would otherwise have had to be excluded from the workshop. Even so, this cost is a heavy item, though the company asks those workers using this special transport to contribute the equivalent of daily travelling expenses by ordinary means—bus, tram or train. A further disadvantage, even of ambulance transport, is the considerable lengthening of the working day which travel involves, since workers living at the periphery of the ambulance run must necessarily leave home a long time before the start of the actual working day.

In the first place, a short list was drawn up from the information given, in conjunction with the job-analysis which formed the basis of selection. The applicants short-listed were then taken by special transport to the factory and interviewed there by a panel of the Medical Advisory Committee. Each man was tried out on each possible job and a final selection made after careful consideration of physical capacity, aptitude and general reaction to the work.

The great majority of the men employed were very severely disabled. Three of the 48 engaged during the first two years had sustained severe gunshot wounds of the head, three gunshot wounds of the spine: four suffered from other spinal conditions. Fourteen had organic disease of the nervous system. Three suffered from heart disease, one complicated by paralysis, and the others with only very limited cardiac reserve. Two suffered from nephritis, one from rheumatoid arthritis, one from congenital muscular wasting and one from cataract of the eye following injury and associated with deafness. Six had lost a leg, usually as the result of war injury, and sometimes associated with other injuries; three had had both legs amputated; and five had sustained severe injuries of hand or arm.

The average age of the men was thirty-two years. Twenty-five were married. Four of the men travelled to the workshop in motor chairs, one came in his own car, and fifteen required special ambulance transport; two or three others who did not necessarily require such special transport but who happened to live on the ambulance routes, were conveyed to work by ambulance.

The following examples will serve to illustrate the type of workmen employed in the workshop:—

(a) Ex-serviceman, aged 23. While serving in Italy in 1944 received a gunshot wound of the spine and, as a result, a spinal cord injury—at first complete, but recovering to some extent, though leaving marked spastic paralysis of both legs. He was for a time unable to walk, but following several operations was enabled to get about with the aid of two sticks, wearing a raised boot on the left side. He travels to the workshop in his motor chair. Previously a tyre-worker, he is now employed as a machine operator, the standard machine having been modified to suit his disability. Days work lost, 20 out of 486. This man's whole demeanour has changed since he came to work at Hillington: originally very bitter, he is now much more sociable and has developed a flair for the accordion, playing in the works orchestra.

(b) Age 38. Suffers from disseminated sclerosis. First symptoms, weakness of legs and loss of sight of right eye, appeared in 1936. Now gets about with extreme difficulty, with partial paralysis of his legs. Served his apprenticeship as a joiner, but had not worked for a long time : is employed here as a machinist. Days work lost, 18 out of 486. Formerly he had to be carried up and down the stairs of his tenement house, and though he has recently been more suitably housed he still has to be brought to the workshop by ambulance ; he is very prone to fall. Cheerful and a hard worker, he has undoubtedly been helped considerably by employment here.

(c) Age 23. Spastic paralysis of the left side with deformity of left foot, result of birth injury. There is also excessive fragility of the bones with the result that he has had about thirty fractures, chiefly of the left arm and left leg. He is deaf. This man has spent much of his time in hospital and has had very little education, partly because of his congenital deafness. He has to be led by the hand, and is brought to work by ambulance. He had never worked before coming to Haven Products and is employed here in trimming and cleaning the blankets before packing. He is very happy to be working, and his parents are very pleased. Days work lost, 24 out of 448.

## 5. THE SUCCESS OF THE VENTURE

The success of the venture can be judged by several standards—the regularity of attendance of the men, the output, the financial stability of the enterprise, and, perhaps most important of all, the effect on the men themselves of work in the sheltered workshop.

Taking the shop as a whole, the overall absence of the workers from all causes, sickness and other, amounted to some 7·5 per cent. of the total number of working days. There has been considerable variation in absence from month to month, and this has inevitably raised production problems for the manager of the shop, himself a disabled man. Some of the men had virtually no absence over the entire period of two years.

The output of the workshop was low in the early months, as was only to be expected from an entirely new trainee staff of severely disabled men. The curve, however, rose gradually upwards, with minor set-backs due to modification of the working cycle and inevitable difficulties in maintaining a steady stream of raw material : after seven or eight months, production became fairly stabilised at a satisfactory level.

From the start it was accepted that the workshop must be conducted on lines financially sound. Only so could there be any certainty of survival of the enterprise : it was firm policy to avoid deficits. There can be no doubt that this policy was sound and that it has been appreciated by the men, for they have the satisfaction of knowing that they are in fact earning their wages and that in the enterprise there is no element of charity. As has been explained, the company does not operate for profit to its shareholders, and the directors consider that the financial results show a sufficient margin to justify reasonable confidence in the continued success of the enterprise.

The best testimony to the value of the workshop is the very striking change which has taken place in the men themselves. Most of them are obviously thrilled to be able to work again, and there is about the atmosphere of the workshop a happiness, an enthusiasm and a sense of corporate life that is quite unmistakable. Many visitors to the factory have commented upon its happy atmosphere. The specialist physicians and surgeons, on the occasion of their annual review of patients, have often remarked on the favourable influence of employment in the workshop on the clinical progress of the patients.

Altogether nine of the men who were taken into employment in the sheltered workshop gave up work there. Occasionally the man improved and was able to leave the sheltered workshop to take up a better job. One worker, a man with severe gunshot wounds of the head, was improving during his stay in the workshop, but did not like inside work, especially in hot weather. He had been a slater and left the workshop to return to work as such with a firm in the country where his brother was employed as foreman. The nature of his disability made it dangerous for him to work where there was a danger of falling, and he would undoubtedly have been better to have remained at Hillington. Another man, a good worker, left without having secured another job. He was a capable and willing man who had been a barman before the war and he felt that he was capable of doing work that would bring him higher wages.

One of the workmen died. He was a young ex-serviceman who had had both legs amputated above the knee on account of war injury. He fell ill and was forced to stop work at the end of 1946: six months later he died of pulmonary tuberculosis.

Three other men never really settled in the workshop, though one of them worked there for ninety-nine days. He had a gross disability—unsteady gait together with loss of sensation and loss of power in his right hand. He found it difficult to adapt himself to his disability; he was of the foreman type, and it irked him that he was no longer able to hold a responsible job. He became rather a disturbing element in the workshop, left in a violent temper, and has been unemployed ever since. The others worked at Hillington for only two and three days respectively. One had sustained a serious injury to his right hand in the North African campaign and had also become completely unbalanced. He was tried in the workshop rather against the better judgment of the selecting panel. It very soon became apparent that he could not work along with his fellow-workers in the shop. He went to Birmingham in search of work, but has since returned to Glasgow and is still unemployed. The other man who left the workshop suffered from cerebral tumour. He had been idle for a long time and was very anxious to start work, but he was subject to headaches on stooping, and though he liked working at Hillington, he thought that stooping over his work-bench would aggravate his headaches and after three days decided to leave.

## 6. SUMMARY

Experience of two years' working of the sheltered workshop at Hillington has amply demonstrated that many severely disabled men can work successfully under carefully selected working conditions. The work must be such as to afford a reasonable profit margin and compatible with a fair variety of jobs under good environmental conditions. There is reason to believe that, given such conditions, men who are even very severely disabled may be fitted into work at which their productive output stands comparison with that of normal workers. It is true, of course, that a proportion of such men, no matter how anxious, cannot reach an economic level ; so it is essential to build up a carefully balanced team. The precise balance of the team will fall to be determined in the light of the needs of the particular job involved. In this workshop it was found that in the manufacture of electrically heated blankets, given a proportion, say up to 20 per cent., of not too severely disabled men, it was possible to blend an economic team of which the remainder could be drawn from among men with severe disabilities—paralysis, disseminated sclerosis, severe gunshot wounds, heart and kidney disease, and the like. In this particular manufacture it was found that the optimum size of team unit was somewhere between 35 and 40.

Much of the credit for the friendly and happy atmosphere of the factory must be attributed to the men themselves. The team spirit was extraordinarily well developed. The men clearly recognised that they were not all endowed with equal capacity for work, but they were prepared to work as a team and to help each other so far as possible. They very soon developed a social club which, in addition to promoting community life and stimulating activity in various crafts, began to evince an interest in wider fields of welfare.

One of the most striking features of this Hillington venture has been the immense measure of goodwill which has permeated it throughout. The tenants on the estate, the Estate Company, medical consultants and social workers in the area, the men themselves, and a whole host of public agencies and private individuals have given tangible evidence of their interest in the scheme and their desire to help. In view of the number of disabled people for whom provision of this kind could profitably be made, it is important to try to harness the great volume of goodwill which has been shown to exist.

Here is surely one of the most practical applications of social medicine : and the success of the Hillington venture indicates that the trading estates now being established up and down the country offer ideal settings for the development of workshops of this kind.

I should like to pay tribute to the enthusiasm and hard work of Miss Elizabeth Turner, then Senior Almoner at Glasgow Western Infirmary, who did so much to make this venture possible.

# THE CARCINOID TUMOUR

## A REVIEW OF SEVENTEEN CASES

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MORGAN (1947) reported a case with a carcinoma of the cæcum and a carcinoid of the ileum, and remarked that the occurrence of a carcinoid with another type of malignant tumour was very rare. The fact that, among 600 autopsies during 1947, we had two examples of carcinoid in multiple tumour complexes made us doubt this statement and decide to investigate the carcinoid tumour further. We soon realised that the significance of the term "carcinoid" had altered since its introduction (Obendorffer, 1907). The purpose of this paper, therefore, is to estimate the malignancy of the tumour and to discuss its nomenclature and occurrence as part of a multiple tumour complex. It will be necessary, in doing so, to refer briefly to the pathogenesis of the tumour.

### HISTORICAL RÉSUMÉ

The principal contributions to our knowledge of the carcinoid tumour have been made as follows :—

- 1838 Merling reported the first case as a carcinoma of appendix.
- 1870 Heidenhain demonstrated the chrome reaction.
- 1888 Lubarsch showed that the tumour probably originated from the crypts of Lieberkühn and regarded it as benign.
- 1890 Ranson reported the first malignant case.
- 1907 Obendorffer reported six appendicular cases and introduced the term "carcinoid."
- 1910 Hubschmann showed that they arose from the "gelben Zellen" (argentaffective cells) of the small intestine and appendix.
- 1914 Gosset and Masson, using a silver impregnation technique, came to a similar conclusion and suggested an endocrine function for the cell of origin.
- 1928 Masson published his later views on the pathogenesis of the tumour.

### PATHOGENESIS

Great confusion exists concerning this tumour and its cell of origin. Some ten theories of origin and thirty different names have been suggested for the tumour, and thirty names for the cell from which

it develops. The principal theories of origin are that the tumour arises from :—

1. Crypts of Lieberkühn (Lubarsch, 1888).
2. Basal cells of the intestinal glands, as in basal cell carcinoma of the skin (Bunting, 1904).
3. Rests of pancreatic exocrine tissue (Trappe, 1907) or islet tissue (Toennissen, 1910).
4. Displaced embryonic glands of Lieberkühn (Abrikossof, 1922).
5. The argentaffine cell of the intestinal mucosa (Hubschmann, 1910; Gosset and Masson, 1914).

Masson (1922, 1924, 1928, 1930), who investigated the subject exhaustively, makes the following points. The axial region of about 86 per cent. of obliterated appendices contains nerves and neuromata partly ensheathed by vestiges of the muscularis mucosa. These neuromata arise from periglandular plexuses and their persistence depends upon their content of argentaffine cells. These cells originate from the epithelium lining the base of the glands of Lieberkühn and migrate into the nerves of the plexuses where they develop argentaffine granules. The cells develop into cylindrical cells and endocrine cells affecting nerves locally. The carcinoid is produced by autonomous proliferation of such argentaffine cells. Masson further states that he has never seen the tumour arising directly from the intestinal epithelium, but always through the medium of a neuroma. Since 1928 the origin of the tumour from the argentaffine cell has been repeatedly confirmed, but less importance has been attached to its association with a neuroma.

*Argentaffine Cell.* The exact *embryology* of this cell is not yet certain. It has a similar *distribution* in all animals investigated and is present throughout practically the whole intestinal canal. It is most numerous in the duodenum, decreases distally, and is very uncommon in the colon, save in the appendix. It has been described in the pancreas and suprarenals. According to some, it has an inverse distribution to the Paneth cell. *Morphologically* the cell is typically single, variable in shape, lies on the intestinal basement membrane and has an attenuated apex reaching the lumen. The nucleus is central, round, vesicular, and has a distinct membrane. The cytoplasm contains prominent granules which vary in size and number and lie in the basal region of the cell. The granules have at least fourteen staining reactions, the most important being pink with eosin, black with silver impregnation (Gosset and Masson, 1914) and brown with potassium bichromate (Heidenhain, 1870). Sometimes the cell shows vacuolation which may be a phase in the life cycle of the granules. There has been some debate as to whether the cell contains lipid.

Various theories have been put forward to explain the *function* of the cell, particularly regarding the significance of the granules. The cell has been regarded as non-secreting but concerned with absorption (Kultschitzky, 1897), in which case the granules may be



artefacts (Eklof, 1914) or permanent bodies such as occur in leucocytes or nerve cells (Masson, 1922). Other authorities have considered that the cell produces a secretion which may be discharged into the blood stream to assist in carbohydrate metabolism (Eros, 1930) or hæmopoiesis (Jacobson, 1939), or which may act locally on nerves in the wall of the gut (Masson, 1924). None of these theories has received general acceptance, so that the exact function of this cell is unknown.

### NOMENCLATURE

Eponyms should not be used in scientific terminology, so, in the absence of accurate knowledge of the function of the cell of origin, the tumour must be described in terms of the staining reactions of this cell, of its anatomical distribution or of some peculiar property of the tumour itself. Macklin and Macklin (1932) refer to the popular current terms—"enterochromaffine," "argentaffine" and "basi- or basal granular" and prefer the first since it indicates the site and an important staining reaction. It is still necessary, if this term is used, to name the part of the alimentary canal under consideration so that the term is redundant and unwieldy. The term "argentaffine" also describes an important staining reaction and is shorter. This reaction, however, is very variable and we have been unsuccessful with a variety of techniques after Helly or Kaiserling I fixation. Our material has not been suitable for the method recommended by Dawson (1944) and Sharples (1945), nor have we been able to try that suggested by Gomori (1948). Hence, we do not feel that the use of this term is justified. We do not favour the term "basal granular" since this is not the only cell with basal granules.

The term "carcinoid" was coined by Obendorffer (1907) to indicate a tumour of carcinomatous type, but without invasion or metastasis. The cases which Obendorffer described all presented early because of obstruction and had not time to metastasise, but lymphatic embolism in the muscularis was evident in some of them. There is no doubt that the tumour we discuss is the same as that described by Obendorffer, and, since his term has priority and is concise, we shall use it here.

### MATERIAL AND CASE NOTES

Our material consists of 17 cases which have occurred in the routine autopsy and biopsy work in Edinburgh Royal Infirmary (1932-1947), Leith Hospital (1940-1947) and the Edinburgh Municipal Hospitals (1936-1947). During these periods 10,192 autopsies were performed and 21,947 biopsies from the Infirmary and Municipal Hospitals were examined (figures for biopsies from Leith Hospital are not available). Brief details of the cases are contained in the Table: further particulars of Cases 4 and 11 are given below, and of Cases 5, 6, 14 and 15 in the discussion on multiple tumours.

## THE CARCINOID TUMOUR

TABLE

Original Pathological Report.				Presenting Feature.		Treatment.		Result.		Original Pathological Report.	
Case.	Sex.	Age.	Duration of Symptoms.	A. APPENDIX		B. SMALL INTESTINE		C. STOMACH		D. CACUM	
				Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
1	M.	17	Two days	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
2	M.	19	Recurrent present attack ten days.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
6	M.	48	Recurrent present attack fifteen hours.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
7	- F.	48	Three days.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
10	F.	20	One day.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
12	F.	18	One day.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
3	F.	67	Two months.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
13	M.	47	One day.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
14	M.	72	Death from carcinoma of head of pancreas : Carcinoids found at autopsy in jejunum and upper ileum.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
15	M.	83	Three weeks.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
16	M.	61	Six weeks.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
17	M.	73	Death from Weil's Disease : two carcinoids found at autopsy in upper ileum.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
5	F.	74	Death from carcinoma of jaw : carcinoid of stomach found at autopsy.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
11	M.	65	Two weeks.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
9	M.	73	Nine months.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.
4	M.	64	Six months.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Obstruction.	Incontinence of bowel.	Diarrhoea.

Note.—The cases are grouped according to the site of the tumour or main tumour. Where the result is given as "Cure" no follow-up details are available: in cases where the patient is described as "alive and well," reports were obtained from the family doctor at the time of writing the paper.

CASE 4.—A clinical and radiological diagnosis of carcinoma of the pelvic junction was made, but at operation numerous "carcinomatous" nodules studded the peritoneal cavity and coils of intestine. The piece of omentum examined showed "a malignant carcinoid."

CASE 11.—At autopsy a large diverticulum on the lesser curvature of the stomach contained what appeared to be a fungating carcinoma: histological examination, however, showed a benign leiomyoma. No other tumour was found in the bowel, but a single nodule in the liver had the microscopic structure of a carcinoid. In the absence of any other primary tumour, it is probable that the growth in the stomach was a carcinoid and that the block taken for examination came from an area of muscle hypertrophy such as commonly occurs with these tumours.

### DISCUSSION

The *sites* in which the carcinoid tumour has been reported are those where the argentaffine cell occurs, save in the duodenum. It is most common in the appendix, next most common in the small intestine, the ileum being more often affected than the jejunum: other sites include the stomach, large intestine, pancreas, Meckel's and other

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FIG. 1.—Appendix (Case 1). Genesis of carcinoid from glands of mucosa. Normal gland at bottom right and upper margin with gradual transition to tumour at bottom left ( $\times 140$ ).

FIG. 2.—Jejunum (Case 13). Cytology is fairly uniform but there are frequent mitotic figures, especially at centre ( $\times 450$ ).

FIG. 3.—Cæcum (Case 9). Carcinoid showing marked irregularity of cytology ( $\times 250$ ).

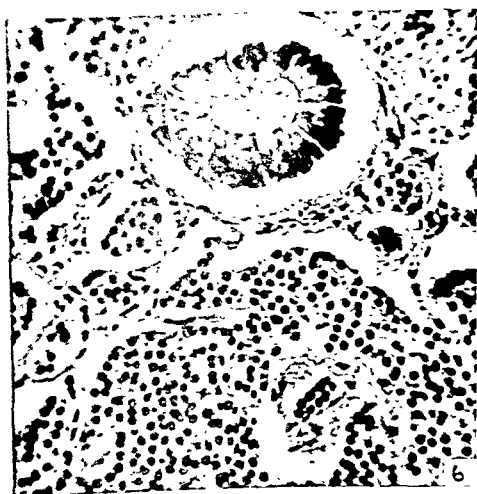
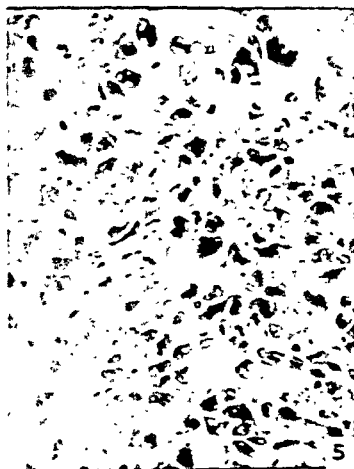
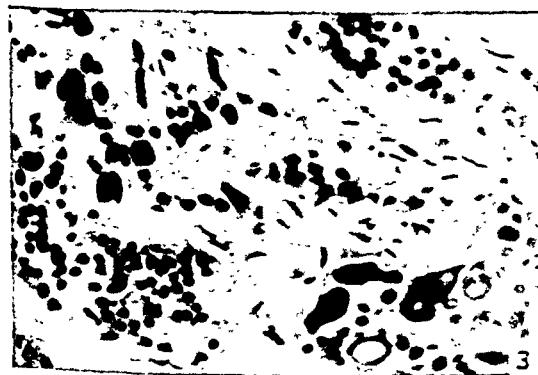
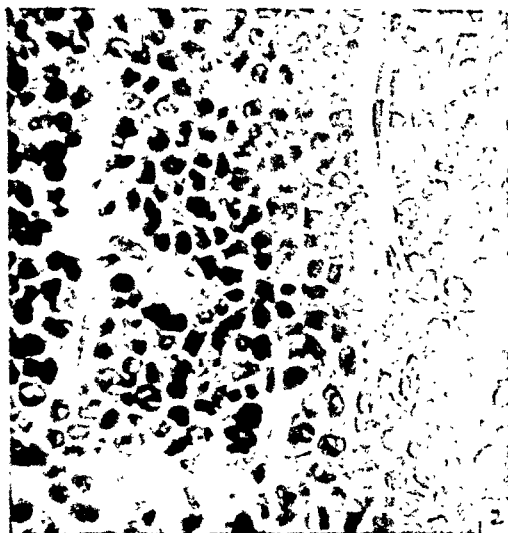
FIG. 4.—Liver (Case 8). Venule in portal tract at margin of carcinoid metastatic deposit containing clumps of tumour cells ( $\times 140$ ).

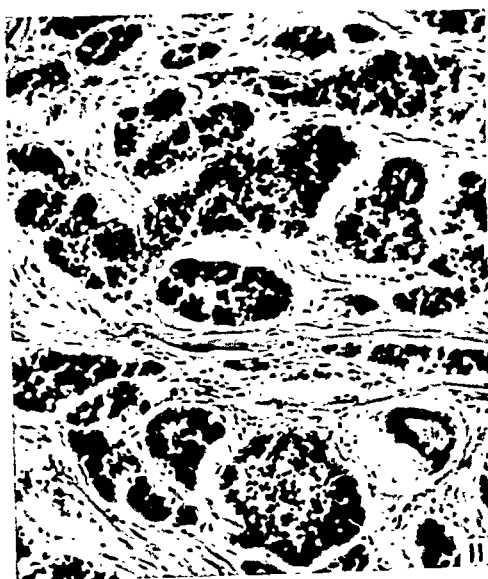
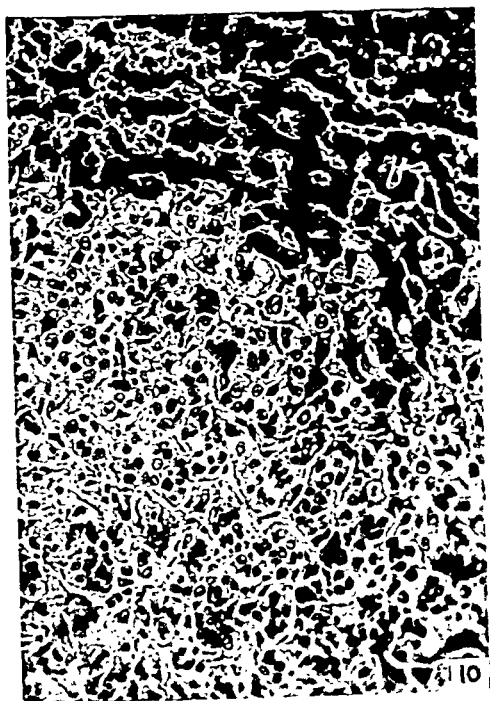
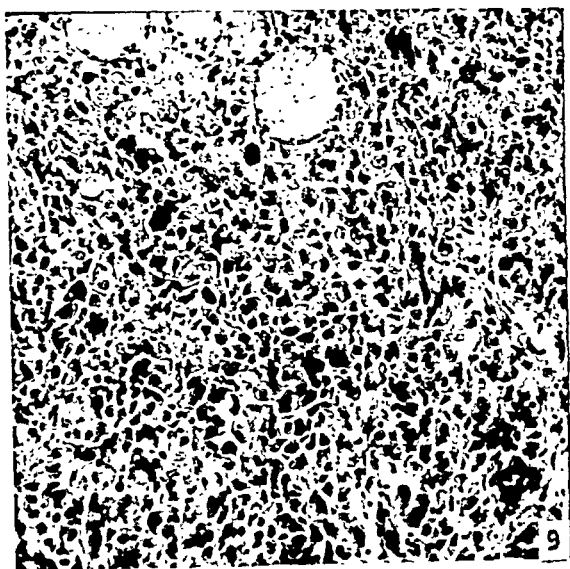
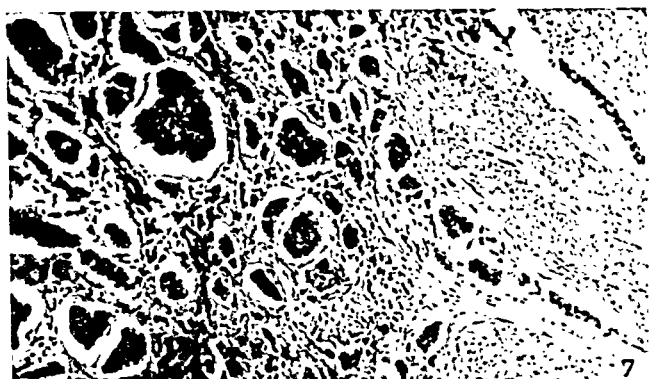
FIGS. 5 and 6.—Case 5. Sections from anaplastic carcinoma of jaw (Fig. 5,  $\times 300$ ) and carcinoid of stomach (Fig. 6,  $\times 250$ ).

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diverticula, and gall-bladder. In 15 of our 17 cases the site of the primary tumour is known: six (Cases 1, 2, 6, 7, 10 and 12) were in the appendix, six (Cases 3, 13, 14, 15, 16 and 17) in the small intestine, two (Cases 5 and 8) in the stomach and one (Case 9) in the cæcum.

Frequently *several* nodules can be regarded as primary growths. This is more common with the intestinal than with the appendicular tumour, some 25 per cent. of the former having more than one nodule of equal size. The current opinion (Dockerty and Ashburn, 1943), is that all tumours occurring in the same or adjacent segments of the intestine are multiple primary foci. These authors do not define "segments of the intestine" but it is reasonable to assume that all intestinal tumours of the same size, are primary foci (Cases 14, 15 and 17). Willis (1940) reported cases of solitary or multiple intestinal tumours with "metastasis" to the pancreas, stomach and gall-bladder, and suggested that nodules in these sites may be regarded as further primary foci, since the argentaffine cell does occur in these organs. The number of nodules in the small intestine may vary from one to over sixty. Thus Case 14 had five widely scattered in jejunum and ileum and Case 15 had a single nodule in the stomach and many in both small and large intestine, particularly in the ileum.





The *effects on the bowel* of a carcinoid depend largely on its site, the main difference being between a tumour in the appendix and one in the intestine. The smaller tumours occur as nodules or plaques within the bowel wall, projecting towards the lumen and are usually covered with intact mucous membrane. As they enlarge, they protrude further into the lumen but remain sessile, so that obstruction by mere mass of tumour is more likely in the narrower appendix. The symptoms arising from obstruction are the commonest presenting features of a carcinoid, occurring in five of our six appendicular cases. Obstruction of the small intestine by mere mass of tumour has not to our knowledge been recorded, but the fibrous and muscular reaction to the growth may cause stenosis of the lumen. We stress this point because we believe that many of these tumours which, by reason of obstructive symptoms are removed before they have shown metastasis, would have progressed to the frankly malignant stage if left. An analysis of 119 reported cases of carcinoid, all but ten of which have appeared since Cooke's review (1931), shows that the average age of 49 obstructed intestinal cases was 57.2 years: in 21 non-obstructed intestinal cases with metastasis it was 60.6 years. Many of the latter cases were

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FIGS. 7 and 8.—Case 15. Sections from carcinoid of ileum (Fig. 7,  $\times 80$ ) and carcinoma of descending colon (Fig. 8,  $\times 80$ ). Note the invasion of the muscularis on the right of Fig. 7.

FIGS. 9 to 11.—Case 14. Sections from carcinoma of pancreas (Fig. 9,  $\times 140$ ), hepatoma in liver (Fig. 10,  $\times 140$ ) and carcinoid of ileum (Fig. 11,  $\times 80$ ).

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found at autopsy in patients dying from other causes, so that these results are not significant. Insufficient cases of malignant carcinoid of the appendix are recorded to make a similar analysis possible. Cooke found obstruction in 17.4 per cent. of the 115 intestinal cases which he analysed. It occurred in four of the six intestinal cases in our series (Cases 3, 13, 15 and 16), and in 41 per cent. of the 119 cases which we have analysed.

One appendicular carcinoid in the present series (Case 7) was, we believe, unique in that it presented as a strangulated femoral hernia, the sac of which contained the appendix with a carcinoid tumour. The occurrence, as in Case 13, of perforation in the presence of a solitary nodule in the jejunum (see Fig. 12) is unusual, but has been reported by Cooke.

The *microscopic picture* of the carcinoid is usually quite characteristic and has been described frequently in the past. We will deal only, therefore, with those features in our cases which are relevant to the present purpose. The microscopic findings vary considerably even in different areas of the same tumour, but the cytological and morphological appearances are those of a tumour of glandular origin. Evidence of genesis from the appendicular epithelium can be seen in Case 1 (Fig. 1). Origin of the tumour from argentaffine cells could not be demonstrated since neither the argentaffine cells of the normal mucous

membrane nor the cells of the tumour could be stained with silver. The majority of the tumours consist of uniformly small polyhedral cells, but varying degrees of pleomorphism are seen, so that some tumours are locally anaplastic (Case 9, Fig. 3). Mitotic figures are difficult to find in the more uniform tumours, but in others are numerous (Case 13, Fig. 2). These two features do not necessarily occur together or represent absolute criteria of malignancy, but are indications that growth may be rapid.

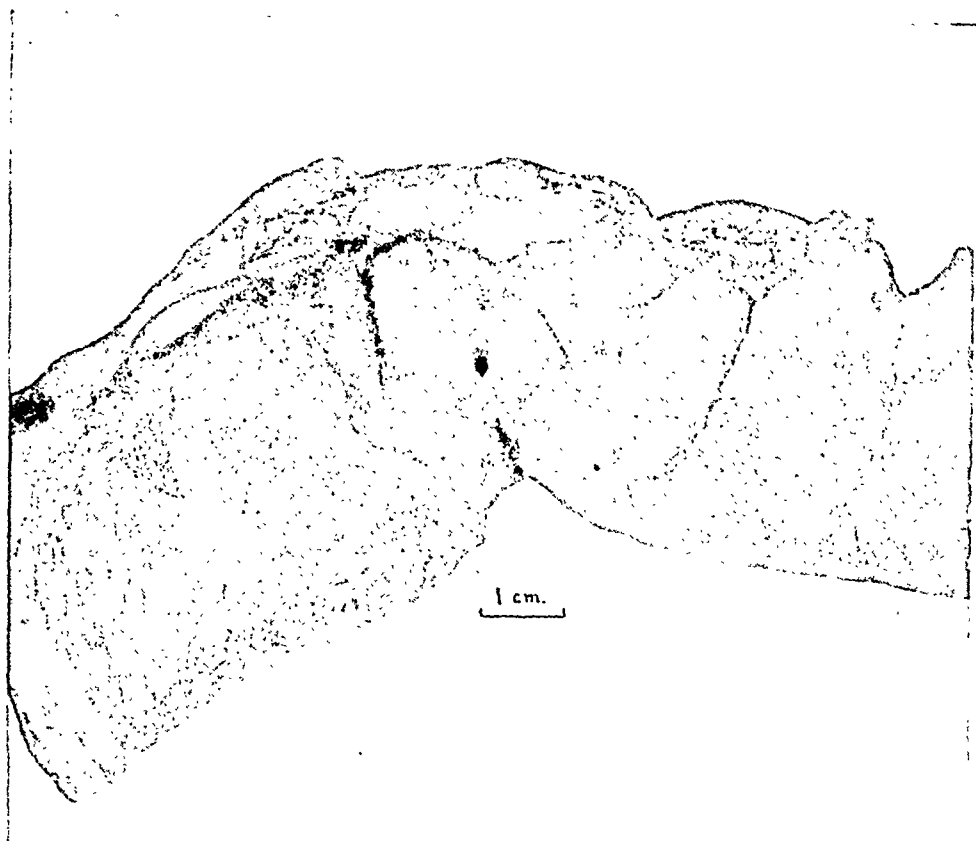


FIG. 12.—Jejunum (Case 13). Carcinoid (centre) with circular perforation and serofibrinous exudate on peritoneal surface.

The cells in many of the nodules are confined to the mucous and submucous coats, but evidence of infiltration into and through the muscularis is commonly seen even in small and cytologically uniform tumours. These nodules, though macroscopically apparently circumscribed, rarely, if ever, have a capsule or pseudo-capsule as found in the benign adenomata. Further evidence against considering either the smaller or apparently innocent larger growths as benign is the not infrequent occurrence of lymphatic or vascular embolism (Case 8, Fig. 4). Indeed, it is surprising that more extensive metastasis than to regional lymph nodes and liver is not more common. This is probably because the tumour is normally slow-growing, even in cases with

metastatic deposits. In this connection Dockerty and Ashburn report that not less than 33 per cent. of cases are alive eight years after operation for such a tumour.

When *metastasis* occurs, the secondary deposits show much the same distribution as in adenocarcinoma of the bowel, so that regional lymph nodes and liver are most frequently involved. In the literature, the interpretation of "metastasis" is subject to as much variation in connection with the carcinoid as with other tumours, so that some cases reported as showing metastatic deposits in the mesentery and regional lymph nodes are examples of direct spread. However, some of our cases with regional lymph node and mesenteric involvement have deposits in para-aortic glands which we consider to be examples of lymphatic metastasis. Though the regional nodes and liver are the only sites of metastatic deposits in this series, hæmatogenous spread may occur to such sites as the suprarenals, kidneys, subcutaneous tissue and brain (Willis, 1940), and the spleen (Ritchie and Stafford, 1944). Lymphatic spread may reach the mediastinal glands or testis (Cope, 1929). Metastasis occurs more frequently from a primary tumour in the small intestine than from any other primary site, the figures given by Willis (1934) being up to 20 per cent. from the intestinal tumour and about 6 per cent. from the appendicular growth (this figure, quoted by Willis, is only an approximation). Ritchie and Stafford have since then reported "metastasis" in 126 (37·9 per cent.) of 332 cases of intestinal carcinoid. This figure is subject to the criticism of "metastasis" already noted.

#### OCCURRENCE OF A CARCINOID IN A MULTIPLE TUMOUR COMPLEX

As previously mentioned, one reason for our interest in this type of tumour was the paper by Morgan (1947) in which a case similar to our Case 15 was recorded. His patient had a large fungating carcinoma of the cæcum with spread into the pericolic fat, but no distant metastasis, and a carcinoid five feet from the ileo-colic valve with invasion of the muscle coat and "metastasis" in three mesenteric nodes. Though our own series is small, we do not agree with Morgan's statement concerning the occurrence of a carcinoid along with another malignant tumour, since three of our 17 cases were associated with other primary malignant tumours (Cases 5, 14 and 15). We have used the criteria of Warren and Gates (1932) in assessing multiple malignant tumour complexes.

CASE 5.—Clinical diagnosis:—Carcinoma of left jaw. The growth in the jaw proved on microscopical examination to be an extremely anaplastic carcinoma (Fig. 5): no metastatic deposits were found. An incidental finding at autopsy was a small grey submucous plaque in the fundus of the stomach measuring 8 mm. in diameter. Microscopically it was a carcinoid with no evidence of malignancy and quite different from the alveolar tumour (Fig. 6).



CASE 14.—Clinical diagnosis:—Carcinoma of head of pancreas. At autopsy there was a large growth in the head of the pancreas and other deposits in the liver, pancreatic lymph nodes, right lung and small intestine. The intestinal deposits were five widely separated small nodules, two in jejunum and three in ileum: all were apparently confined to the mucosa and sub-mucosa, the largest, in the lower ileum, being ulcerated. The clinical diagnosis was confirmed and all other deposits were considered metastatic. Histological examination revealed the pancreatic tumour to be a rapidly growing, undifferentiated carcinoma (Fig. 9), one section of liver showing a metastatic deposit. A further section of liver contained a small tumour of entirely different appearance—a liver-cell carcinoma (Fig. 10). Section of one of the nodules in the small intestine showed a typical carcinoid (Fig. 11).

CASE 15.—Clinical diagnosis:—? Intestinal obstruction. At autopsy many small nodules 0.5 to 7 cm. in diameter projected into the lumen of the gut from mid-jejunum to pelvi-rectal junction, being most numerous in the upper ileum. Two larger masses, 1.5 cm. in diameter and 15 cm. apart, at the junction of upper and middle thirds of the ileum, had caused "fibrosis" with narrowing of the lumen by half. Many slightly enlarged lymph nodes were present in the ileal mesentery, and the liver contained very many small deposits. A single nodule 0.5 cm. in diameter was present on the gastric side of the pylorus. The diagnosis made at autopsy was "multiple sarcomatosis of the intestine with secondary deposits in mesenteric lymph nodes and liver." Histological examination of a nodule from the small intestine, a mesenteric lymph node, and the liver all showed a typical carcinoid (Fig. 7), but a section from a nodule in the large intestine showed a columnar-cell adenocarcinoma (Fig. 8).

We have not included case 6 where a proven carcinoid in the appendix was said to be associated with a carcinoma of the ascending colon, since no material is available to confirm the clinical diagnosis of the second tumour.

### CONCLUSIONS

We believe that every carcinoid tumour is a slow-growing malignant neoplasm of carcinomatous type. This holds good despite the relatively favourable prognostic outlook as shown by survival up to 20 years with deposits left *in situ* (Mallory, 1940), and an original pathological report of a "benign" carcinoid. The impression gained from an extensive search of the literature is that a carcinoid is no more unusual than any other tumour in a multiple tumour complex. We favour the continued use of the term "carcinoid" in the absence of a satisfactory specific name and until more is known of the derivation and function of the cell of origin.

### SUMMARY

1. A résumé of the history of the carcinoid tumour is given.
2. The pathogenesis and nomenclature are discussed, with reference to the argentaffine cell.

3. Seventeen cases in stomach, intestine, and appendix are reviewed, genesis of the tumour from appendicular epithelium being illustrated.
4. Two unusual examples are recorded, one in a strangulated femoral hernia and one in jejunum with perforation.
5. Three cases occurring as part of a multiple tumour complex are described.
6. The malignant nature of this tumour is emphasised.

We wish to acknowledge the help and encouragement which we have received from Professor A. Murray Drennan and Dr R. F. Ogilvie. Our thanks are also due to Dr A. C. P. Campbell for help in translation, to the Physicians and Surgeons concerned for access to their cases, to the Doctors who supplied follow-up notes and to Messrs T. C. Dodds, J. Blackley and J. Waugh for their help in the technical work. Histological material for Cases 13 and 16 was supplied by the Royal College of Physicians Laboratory.

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# CLINICAL TRIALS OF ANALGETICUM NU 896 AND OF AMIDONE

By A. J. GLAZEBROOK

A POWERFUL analgesic is required free of the undesirable attributes of products derived from the poppy. The work of Schaumann (1940) on the compounds produced from the 4-phenyl-piperidines synthesised by Eisleb (1941) opened the way for a more rapid growth of the conception that analgesic activity can be related to chemical structure and led to the introduction of pethidine. A similar line of investigation with amidone and related compounds (Thorp and others, 1947) showed that the butyl-ethyl ketone and the dimethylamino side chains were the essentials for its analgesic activity. Bergel and his colleagues (1944, 1946) have further explored pethidine derivatives and related compounds, and came to the conclusion that the shape or fit of the molecule as a whole was more important in determining its analgesic activity than any one precise duplication of fractions of the morphine molecule. Many new analgesics have thus been synthesised.

The present paper is concerned with the clinical value of analgeticum NU 896 and of amidone. Analgeticum NU 896 (1-isopropyl 4-phenyl 4-propionoxy piperidine hydrochloride) is related to pethidine, and is not at present marketed. Amidone (*dl*-2-dimethyl amino-4 ; 4-diphenyl heptan-5-one hydrochloride) is marketed in Great Britain under the trade name of physeptone.

## METHODS

Pain threshold determinations were made in 86 adults, and changes made in the threshold after the injection of morphine, pethidine, and analgeticum NU 896 recorded. Amidone was not available at first, but was also injected into 49 of the subjects.

The analgesic power of morphine, amidone, and analgeticum was compared in 110 patients suffering from acute pain. Nine of them had colic—biliary and renal—the remainder had experienced severe and intractable pain for a considerable time, and for the most part consisted of patients with incurable malignant disease and chronic rheumatism. Injections of each of the drugs were made on different days, with from two to seven days interval between each injection. The patients were observed for two hours after the injection, and questioned the following day as to its efficacy.

Morphine, amidone and analgeticum NU 896 were given by mouth to 52 patients with chronic pain. Most of them had incurable malignant disease. Three had post-herpetic neuralgia, and X-ray treatment had failed to relieve them. The drugs were administered in turn for fourteen days. A comparison having been made, the administration of amidone or of NU 896 was continued where possible over a period of at least three months.

Work with animals had indicated that the therapeutic dose of analgeticum NU 896 in an adult was likely to be about 25 mgms. This amount was usually prescribed, and compared with 16 mgms. of morphine, 5-15 mgms. of amidone, and 50 mgms. of pethidine.

The investigation was commenced early in 1946, and continued over the next two and a half years.

### PAIN THRESHOLD DETERMINATIONS

There are several experimental methods of comparing the analgesic powers of drugs in human beings. These employ the pain of mechanical, thermal or electrical stimulation of the skin or gums; or of artificially-produced muscle ischæmia.

Too much reliance must not be placed on such methods. They attempt to determine quickly the analgesic potency of a drug which can really only be found by prolonged observations upon patients with severe pain over a period of time.

Most of the patients used in the present work were old and frail, and elaborate techniques of estimating pain thresholds were unsuitable. Methods employing heat are particularly inappropriate, as the presence of chronic severe pain not infrequently results in an increase of the pain threshold, and there is a risk of heat damage to the skin. It has also been my experience that when experimental drugs are injected into human subjects while tests are being carried out on them, side effects are exaggerated and sometimes described when it is hardly possible that they exist, as, for example, when quite innocuous substances are used as controls.

The pain threshold device used in this work has already been described (Glazebrook and Branwood, 1945). A blunt metal pin is gently pressed into the tibia by a screw, until the subject complains of pain. The pressure of the pin on the bone is communicated by means of a rubber diaphragm and rubber tubing to an ordinary sphygmomanometer gauge, and read off in mm. Hg.

All the drugs were given by hypodermic injection, and twenty-four hours rest was allowed between each injection. The pain thresholds were read off at half-hourly intervals after each injection. The results are given in Table I.

TABLE I

Drug.	Mean Increase in Pain Threshold (mm. Hg.). After Injection.				No. of Cases.
	$\frac{1}{2}$ hour.	1 hour.	1½ hours.	2 hours.	
Pethidine 50 mgms. . .	4·7	4·9	3·0	1·2	86
Amidone 10 mgms. . .	7·4	8·2	10·1	5·3	49
Morphine 16 mgms. . .	7·7	8·7	11·3	6·7	86
Analgeticum NU 896 25 mgms.	8·1	9·5	11·8	7·6	86

The results suggest that analgeticum NU 896 25 mgms. has a more profound and prolonged analgesic action than 16 mgms. of morphine, or of 10 mgms. of amidone.

### CLINICAL COMPARISON OF ANALGESIC ACTIVITY (HYPODERMIC INJECTIONS)

One injection each of amidone 10 mgms., of morphine 16 mgms., and of analgeticum NU 896 25 mgms., was made into 110 patients suffering from severe pain. The results are given in Table II.

TABLE II

Drug.	Number of Cases Admitting.		
	Marked Relief.	Some Relief.	No Relief.
Analgeticum NU 896 25 mgms. .	105	5	0
Morphine 16 mgms. . .	99	20	1
Amidone 10 mgms. . . .	92	21	7

The duration of the analgesia resulting from a single injection of analgeticum NU 896 was usually about eight hours, but was sometimes remarkably prolonged, instances of twelve to eighteen hours not being uncommon. That of amidone was about four hours, occasionally being prolonged to ten hours, with morphine occupying an intermediate position.

### SIDE EFFECTS AFTER HYPODERMIC INJECTION

(a) *Respiratory Depression*.—Table III shows the effects on the respiratory rate caused by the drugs.

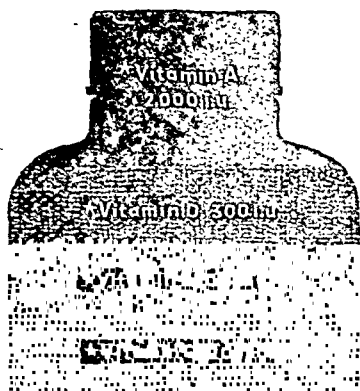
TABLE III

Drug.	Percentage of Cases in which Depression of Respiration Occurred.	Mean Depression of Respiration. After Injection. (Respirations per Minute).			
		$\frac{1}{2}$ hour.	1 hour.	$1\frac{1}{2}$ hours.	2 hours.
Analgeticum NU 896 50 mgms. (26 cases).	100	3.5	4.1	4.0	3.0
Analgeticum NU 896 25 mgms. (110 cases).	58	2.4	2.5	2.6	2.1
Amidone 10 mgms. (110 cases)	30	1.9	1.9	2.0	1.5

Although amidone caused far less respiratory depression than either analgeticum NU 896 or morphine, in the majority of subjects,

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Fig. 1



Fig. 2

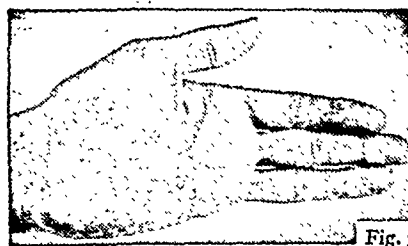


Fig. 3

# REPAIR TO HAND

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A Battle Casualty with considerable destruction of the palm of the hand, the little finger and the fifth metacarpal joint. Skin grafting was carried out as a preliminary measure to produce a healed surface. Later there was excision of graft and scar tissue with application of a direct flap from the back. Fixation was secured with Elastoplast prior to division of the base of the flap.

The details and illustrations above are of an actual case. T. J. Smith & Nephew Ltd., of Hull, manufacturers of Elastoplast, publish this instance—typical of many, in which their products have been used with success.

Fig. 1. Condition on admission.

Fig. 2. After excision of graft and scar tissue. Application of direct flap from the back. Note fixation.

Fig. 3. Flap in position. Full extension of fingers.

Fig. 4. Formation of fist.

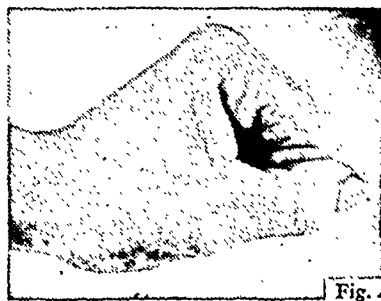


Fig. 4

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occasionally, it had quite a marked effect on the respiration, more profound than that of analgeticum (Table IV).

TABLE IV

*Male Aged 56. Weight 148 lbs. Carcinoma of Tongue, Treated by Radiotherapy*

Drug.	Respirations per Minute after Injection.			
	$\frac{1}{2}$ hour.	1 hour.	1½ hours.	2 hours.
Amidone 10 mgms. . . .	18	16	15	12
Analgeticum NU 896 25 mgms.	16	16	16	15
Morphine 16 mgms. . . .	16	12	16	16

(b) *Euphoria*.—The euphoria produced by analgeticum NU 896 was quite striking in many cases, and sometimes transformed a patient previously dull and listless into a vivacious talker. The sort of remark made by the patients after an injection of 50 mgms. was as follows :—“ A lovely feeling, just like morphine.” “ I am able to sit up and have a good blether after the injection.”

This euphoria, of such immeasurable benefit to the case with incurable cancer, exhausted and mentally dulled by weeks of pain, becomes a dangerous characteristic when the suitability of the drug for curable or non-malignant cases is considered.

Amidone is less likely to cause euphoria, and the euphoria produced by it is of lesser degree (Table V).

TABLE V

Drug.	Percentage of Cases Showing Euphoria after Injection.
Analgeticum NU 896 25 mgms. (110 cases)	35
Analgeticum NU 896 50 mgms. (26 cases)	42
Amidone 10 mgms. (110 cases) . . .	8

There seems little doubt that analgeticum NU 896 used without discrimination in susceptible patients would cause addiction. The same is true, to a lesser extent, of amidone.

(c) *Hyperalgesia*.—Three subjects given 15 mgms. of amidone suffered from a marked exacerbation of their pain about ten minutes after the injection, the exacerbation lasting from five to ten minutes, and being followed by analgesia. This curious effect may be related to the observations made by H. Elliott (1941). He noticed that morphine and pethidine inhibited tissue respiration in brain slices, whereas amidone, in a concentration of 0.005 M. to 0.001 M. caused



stimulation of tissue respiration, afterwards followed by inhibition, in brain slices.

(d) *Other Side Effects of Amidone and Analgeticum NU 896.*—These consisted of sweating, pallor, dizziness, vertigo, swimmy feelings in the head, drowsiness, slight nausea, severe nausea, vomiting and pruritus.

The usual sequence after an injection of analgeticum NU 896 in those patients experiencing side effects was slight dizziness ten minutes after the injection, when the analgesic action was beginning to be felt. This rapidly passed off, being followed by the vaso-motor effects—pallor, sweating—and severe symptoms of marked nausea or of actual vomiting six to eight hours after the injection. No material alteration in the blood pressure was found, in contra-distinction to the well-known action of pethidine, and the cause of the pallor was ascribed to contraction of skin vessels. While the drug rapidly relieved smooth muscle colic, it had no constipating effects.

A similar sequence was seen after an injection of amidone. Initial side effects soon after injection were less common, but nausea and vomiting some hours later was quite frequent. The vaso-motor phenomena—pallor and sweating—were not seen with this drug. The drug was rather less effective in colic than analgeticum NU 896, but did not tend to cause constipation.

The late occurrence of the more unpleasant reactions—nausea and vomiting, six to eight hours after injection of both amidone and analgeticum NU 896 suggest that these are due to breakdown products.

The relative frequency of side effects is given (Table VI).

TABLE VI

*Side Effects*

	Amidone 5-15 mgms. by Injection.	Analgeticum NU 896 25 mgms. by Injection.	Analgeticum NU 896 50 mgms. by Injection.
	Per cent.	Per cent.	Per cent.
No side effects . . . . .	50	15	6
Moderate and transient side effects	22	53	52
Severe side effects (marked nausea, vomiting).	28	32	42

## ORAL ADMINISTRATION

All of the patients, with one exception, preferred the analgesia produced by analgeticum NU 896 to that effected by morphine or amidone. The one exception was a case of carcinoma who had taken morphine for nine months before coming under observation, and he had withdrawal symptoms when the morphine was replaced by either of the other two drugs.

The patients stated that analgeticum NU 896 by mouth gave a

quicker, "smoother," and more complete relief from pain. In cases of really intolerable pain, analgeticum NU 896 afforded a degree of comfort not obtainable with morphine or amidone, within ten minutes of oral administration. The duration of relief from 25 mgms. was from six to twelve hours in the average case. Some had only to take one dose in twenty-four hours to remain relatively comfortable.

As tolerance to the drug became established, the duration of relief lessened, and an increase in the dose sometimes became necessary to 50 mgms. at one time. Such a dose three times daily was sufficient to carry the worst cases of pain on in comfort until death.

Only one case failed to get relief from analgeticum NU 896 given by mouth. This was a man with post-herpetic neuralgia, who had had many forms of treatment before coming under observation, and both morphine and amidone by mouth also failed to relieve him, although he claimed that analgeticum NU 896 by injection helped him.

Amidone 5-15 mgms. by mouth was successful in moderate cases of pain, and was often preferred to morphine because of its relative freedom from causing drowsiness and constipation, but had no advantages over analgeticum NU 896 in this respect. Tolerance to 5 mgms. by mouth was rapidly established—within a few days—and an increase to 10 mgms. became necessary. This level of dosage was often effective for some weeks, but in the worst cases of pain, eventually became useless, and an increase in the dosage above 10 mgms. was not always followed by pain relief, so that it became necessary to change the analgesic to morphine or analgeticum NU 896.

*Side Effects.*—These were the same as those noticed after hypodermic administration. With amidone, cases admitting to no side effects after hypodermic administration, frequently complained of sickness when the drug was given by mouth, and sometimes this sickness was prolonged and unpleasant, lasting for several hours and making the patient really ill. With analgeticum, the effects of oral administration did not differ from those experienced after hypodermic injection.

When oral administration was persisted with, tolerance to the side effects of both drugs usually became established after a few days, and side effects ceased to become troublesome. The side effects, however, in 8 per cent. of the cases given amidone, and in 15 per cent. of the cases given analgeticum, were so severe and so persistent that continued dosage with the drugs was made impossible. Fortunately, morphine gave relief in all of these cases, without unduly disturbing the patient.

#### RELATIONSHIP OF NUTRITIONAL STATE TO PERSISTENT SIDE EFFECTS

The beneficial effect of analgeticum NU 896 in adults harassed by severe and protracted pain was so marked and so superior to that of morphine that it was thought worth while to investigate further

the 8 per cent. of cases who could not take amidone, and the 15 per cent. of cases who could not take analgeticum NU 896, by mouth owing to severe nausea and vomiting. The exhibition of small doses of both drugs, insufficient to provide pain relief, for two to three weeks, did not accustom the patients to them, the side effects occurring immediately the dosage was increased to a satisfactory level.

The patients were aged fifty-two to seventy-eight years old. Many had suffered from malignant disease for a considerable period, and had been subjected to operative procedures, and had had treatment with radium and deep X-ray therapy. Painful conditions of the mouth were quite common, and these had interfered with their nutritional state also.

No relationship was found between the presence or absence of anæmia and the liability to suffer from persistent side effects. Correction of the anæmia did not abolish the tendency to have side effects. Saturation with 1000 mgms. of ascorbic acid, with subsequent daily maintenance dosage of 200 mgms. ascorbic acid, did not prevent the side effects occurring.

#### TOXIC EFFECTS OF AMIDONE AND OF ANALGETICUM NU 896

No deterioration in the blood picture, other than that to be expected in patients dying from advanced malignant disease, was observed in patients given full doses of analgeticum NU 896 (50 mgms. t.d.s.) or of amidone (15 mgms. t.d.s.) over periods of months.

In the early stages of the investigation, before it was realised that analgeticum 50 mgms. six-hourly by mouth was a sufficiency to relieve the most severe examples of pain, a woman with advanced malignant disease having widespread abdominal secondaries was given 75 mgms. analgeticum NU 896 four-hourly. She died after three weeks, and had slight convulsions just prior to her death. The post-mortem revealed toxic changes in the liver and other organs, but no more than to be expected from the presence of malignant disease.

No other toxic changes were encountered during the investigation other than the side effects mentioned.

#### CONCLUSIONS

Analgeticum NU 896, a "piperidine" derivative, has a limited application in the management of patients with incurable malignant disease where pain is extremely severe, as it is capable of affording a degree of relief not obtainable with morphine or with amidone. In such cases, its tendency to produce euphoria instead of somnolence, is usually an advantage, and the patients appreciate its freedom from causing constipation. Patients with painful malignant conditions of the mouth were particularly grateful, as the drug often enabled them to enjoy their food. It gives rise to respiratory depression, comparable to that caused by morphine, and some patients cannot take it because

of its unpleasant side effects. Such actions limit its usefulness. In any case, the marked feeling of well-being which so frequently follows its administration would undoubtedly lead to addiction in susceptible patients.

Amidone frequently gives patients with moderate pain complete relief, with less tendency to cause somnolence than morphine, and little or no constipating effects. Its ability to cause euphoria, much less marked than that of analgeticum NU 896, nevertheless exists. There is thus a liability for it to cause addiction, and discrimination should be exercised in its use. I cannot agree with other writers who aver that it causes fewer side effects than morphine. It gives rise to a lesser degree of respiratory depression, but 8 per cent. of the cases in this series were unable to take it because of severe nausea or vomiting which followed its oral administration. The cases were a selected group of old people with incurable malignant disease, many of whom had been taking morphine prior to coming under observation. Not one of them was intolerant of morphine. It is possible that in four of the cases, the syndrome of nausea and vomiting which occurred when morphine by mouth was replaced by amidone or analgeticum NU 896 by mouth, was a withdrawal phenomenon, and not due to the specific actions of either of the latter two drugs. This explanation, however, cannot apply to others, who had not taken morphine before coming under observation.

Neither analgeticum NU 896 nor amidone are ideal analgesics, and they cannot entirely replace morphine. Constipation is sometimes desirable. Somnolence in a dying patient is occasionally preferable to a wideawake watching and questioning. All three drugs are only too liable to become habit-forming. Finally, there are a minority of patients who cannot take either amidone or analgeticum NU 896, because of side effects, who can be made relatively comfortable with morphine.

The search for an analgesic to replace morphine must continue, and work is now being done with analgeticum NU 1196 (Roche Products) and the Glaxo product, CB 11.

I wish to thank Professor Murray Lyon, in whose wards this work was commenced, and Professor McWhirter, whose co-operation has been invaluable. Messrs Burroughs Wellcome supplied the amidone, and Messrs Roche Products the analgeticum NU 896 and the ascorbic acid.

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## OBITUARY

### GEORGE MACKAY

DR GEORGE MACKAY died at his home in Edinburgh on 10th May 1949. It must rarely have happened that a member of the Honorary Staff of the Royal Infirmary has lived for so long a time as thirty-six years after the termination of a full term of office, as he did. He is survived by few of his contemporaries, and can be remembered, as he was during the active period of his life, only by those of us who have now reached considerable seniority.

He was a grandson of the Colonel George Mackay who raised the Reay Fencibles at the end of the eighteenth century, and a son of Surgeon-General Mackay of the Indian Army. Born near Madras in 1861, he was brought home at an early age, and educated at Clifton and Inverness Colleges. He studied medicine in Edinburgh, graduating M.B., C.M. with Honours in 1883, and M.D. in 1888, being awarded a gold medal for his thesis. He became an M.R.C.S. England in 1883 and F.R.C.S. Edinburgh in 1886, and, deciding to specialise in Ophthalmology, spent some time in Vienna. On his return to Edinburgh, he commenced to practise and was appointed Assistant Ophthalmic Surgeon, and in due course Surgeon to the Royal Infirmary, and Lecturer on Diseases of the Eye in the University. He was, Consulting Ophthalmic Surgeon to the Royal Blind Asylum, Surgeon to the Deaconess Hospital, and held as well a number of other appointments. When he retired from the Infirmary, the claims of a very large private practice did not prevent him from taking up further activities, and among other things he became President of the Royal College of Surgeons and a Manager of the Royal Infirmary. A good many years passed before he retired from private practice, and when he did so, he devoted much of his time to Celtic affairs, in which he took a very deep interest. He was a founder member of the Clan Mackay Society and subsequently the Society's president, seanachaidh and librarian.

In 1930 he was instrumental in arranging for a presentation of a replica of the King's Colour, once carried by the Scots Brigade in the Netherlands. It was deposited in the Scots Church in Amsterdam, to commemorate the officers and men from Scotland, who served in Mackay's Regiment or formed part of the Brigade in the service of the States General from 1572-1782.

Dr Mackay married fifty-three years ago, a daughter of the late Lieut.-Colonel Sir Alexander B. McHardy, K.C.B., and is survived by her and three sons. He was a member of the Royal Company of Archers of the King's Bodyguard for Scotland.

To this formal account of a long and successful career, it is fitting to try to add a description of the man whom we knew best during the active part of his life, most of which he lived before the great divide brought about by the first world war and modern inventions such as the internal combustion engine. We remember a distinguished figure, walking to and from the Infirmary irreproachably dressed, with a well-cut morning coat, shining tall hat, and immaculate linen. A reserved and dignified man, but kindly and courteous to his patients and assistants, considerate and sympathetic with the old and frail. His reputation as a clinician stood high. He had trained

himself with painstaking care in detailed observation of his cases, and his work did a great deal to set the high standard that has always been aimed at in our Eye Department in Edinburgh. As a cataract operator he had no superior and few equals, using the technique of his day with none of the aids to safety that have more recently become so essential, not even bright artificial illumination. He wore no gown or mask, in private operating in his shirt sleeves, and in hospital in a clean white coat. His steadiness and precision were absolute and his results almost uniformly good.

His twenty odd publications consist in the main of reports of unusual and interesting cases.

He represented a type of consultant that we no longer see. *Tempora mutantur et nos in illis mutanum.*

## NOTE

At a meeting of the Royal College of Surgeons of Edinburgh held on 3rd May 1949, Mr Frank E. Jardine, President in the Chair, the following who passed the requisite examinations were admitted Fellows: John Alexander MacLeod, M.D., C.M. UNIV. MCGILL, CANADA, 1941; Harry Guy Antwis Almond, M.B., CH.B. UNIV. L'POOL 1938; John Wilfred Boland, M.B., B.CH., B.A.O. TRINITY COLLEGE, DUBLIN 1938; Alastair Copland Clark, L.R.C.P. & S. EDIN. (TRIPLE), 1940; Mohiy Eddin Abbas El Kharadly, M.B., CH.B. UNIV. CAIRO 1943; Harry Johnson Fisher, M.B., B.CH. UNIV. WALES 1944; Harold Henry Gilbert, M.B., CH.B. UNIV. OTAGO 1939; Henry Allan Graham, M.B., CH.B. UNIV. ST ANDREWS 1925, M.D., 1938; Hrisikesh Hazra, M.B. UNIV. CALC. 1944; Benjamin Joffe, M.B., CH.B. UNIV. CAPE TOWN 1940; Leonard Arthur Key, M.R.C.S. ENG., L.R.C.P. LOND. 1925; Peter Kinnear, M.B., CH.B. UNIV. ST ANDREWS 1939; Thomas Henry Lawton, L.R.C.P. & S. EDIN. (TRIPLE) 1937, M.R.C.O.G. 1947; John Campbell Miller, M.B., CH.B. UNIV. BIRM. 1943; Ian Pinkerton Munro, M.B., CH.B. UNIV. GLASGOW 1940; Abraham Samuel Oscier, M.B., B.S. UNIV. LONDON 1939; Edgar Williams Parry, M.B., CH.B. UNIV. L'POOL 1943; Robert Paul Schach, M.B., B.CH. UNIV. WITWATERSRAND 1944; Archibald James Sinclair, M.B., CH.B. UNIV. GLASGOW 1940; Vincent Tabone, M.D. UNIV. MALTA 1937.

## NEW BOOKS

*The Practice of Industrial Medicine.* By T. A. LLOYD DAVIES, M.D. (LOND.), M.R.C.P. (LOND.). With a chapter on "The Hazards of Coal Mining," by G. F. KEATINGE, M.D. (DUBLIN), D.I.H. Pp. vii+244. London: J. & A. Churchill Ltd. 1948. Price 15s.

The British Medical Association is to follow up a suggestion for a complete medical officer service for the whole industry, made by Sir George Schuster, chairman of the panel on human factors of the Cabinet Committee on Industrial Productivity. This will inevitably mean that large numbers of doctors will have to interest themselves in the special problems of medicine in relation to working conditions. Hitherto the practice of industrial medicine has been limited chiefly to a few whole-time specialists. In the future it seems not unlikely that large numbers of practitioners will have a part-time appointment as a works doctor.

Some conception of the subjects included under Industrial Medicine and their relative importance can be derived from the chapter headings of this book. These are:—Historical and Introductory Survey (12 pages), Medical Examination (20 pages), Accidents, Fatigue and Environment (29 pages), the Social Functions of Industry (24 pages), Industrial Diseases and Toxicology (109 pages), the Hazards of Coal Mining (13 pages), and Workmen's Compensation and Rehabilitation (15 pages).

A doctor, who takes up an appointment in industry for the first time, will have to brush up a part of his medical technique, but perhaps more important, he may have to acquire a new philosophy. In addition to dealing with industrial cases of sickness, he must consider the special biological problems presented by a community held together by a common working purpose and particularly the stresses on health

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resulting from reactions both with other members within the community and with a physical environment, often unavoidably unphysiological. As Chief Medical Officer of Boots Pure Drug Co. Ltd., Dr Lloyd Davies has had a wide experience of these problems. He expounds both the technique and the philosophy of his subject lucidly and concisely and can be recommended to the newcomer in industry as a sound, yet enthusiastic guide.

As usual, the house of Churchill has done its part of the book well and the price is cheap, judged by present day standards.

*Kurze Klinik der Ohren- Nasen- und Halskrankheiten* (A Short Course of Diseases of Ear, Nose, and Throat). By ERHARD LUSCHER, Professor of the University Clinic in Basel. Pp. 513, with 201 illustrations in the text, many in colour. Basel: Benno Schwabe & Co. 1948. Price Fr. 54.

This book—which is written in German, is well produced on good paper, though the type is somewhat thin for easy reading and the frequent use of small type tends to be fatiguing. Illustrations are good, if small, but they are to the point and serve their purpose well.

The book is divided into three main parts Anatomy and Physiology; Methods of Examination and Description of Instruments; Symptomatology and Therapy. The anatomical nomenclature of 1935 is used throughout, but a comparative glossary is included which helps those not accustomed to this terminology.

The section on allergy is the most up-to-date, but in many other parts treatment is hardly in line with modern practice. This is noticeable for example in chemotherapy, and the fenestration operation for otosclerosis.

The author is strongly continental in many of his methods, as in the use of local anaesthesia in operations which in Britain and America are almost invariably carried out under general anaesthesia.

This book is interesting in that it gives a good outline of current practice in a leading Swiss clinic.

*Twentieth Century Speech and Voice Correction.* Edited by EMIL FROESCHELS. Pp. 321. New York: Philosophical Library. 1948.

The literature of speech therapy is steadily increasing, but there is still plenty of room for such sound scientific teaching as this book contains. The name of Professor Froeschels as editor is a sufficient guarantee of excellence, and the editor is ably supported by a team of eighteen experts, each a specialist in his or her own field. Professor Froeschels himself contributes the introductory chapter on Anatomy and Physiology, while other chapters from his pen deal with the Prosthetic Therapy of Cleft Palate, and with the Pathology and Therapy of Stuttering. The latter chapter, although it runs to only fourteen pages, with no less than 87 references, gives, as in a nutshell, the main features of this common disorder, and includes a description of Froeschels' "chewing" method of treatment which certainly deserves greater publicity than it has hitherto received. This chapter alone is worth the price of the whole volume, but the other chapters are full of sound advice and teaching. Among the subjects mentioned are Aphasia, Alalia, Dyslalia, and Rhinolalia, but a simple and straightforward nomenclature is followed, and the volume, despite its composite authorship, is free from that bias of view and complexity of classification so common in books on speech therapy. An interesting and useful aspect of this volume is the inclusion of six chapters, in a total of twenty-two chapters, devoted to various aspects of Education of the Deaf and Rehabilitation of Hearing. The work of the teacher of the deaf and that of the speech therapist are still far too widely separated, at least in Britain, and this union is a move in the right direction.

As the title implies, this is a summary of the latest views on the correction of speech disorders, and it may be cordially recommended to teachers and physicians alike, and indeed to all who have to deal with the impediments of voice and speech.

*A Surgeon's Guide to Local Anaesthesia.* By C. E. CORLETTE, M.D., CH.M. (SYD.), F.R.A.C.S. Pp. xi+355, with 200 illustrations. Bristol: John Wright & Sons Ltd. 1948. Price 35s. net.

This book has as its secondary title "A Manual of Shockless Surgery," which indicates unequivocally the author's enthusiasm for local anaesthesia. Most readers will agree with his general thesis that nerve-blocking has many advantages over generalised intoxication by inhalational or intravenous agents.

The prime virtue of Mr Corlette's book is its practical basis and his long experience of local anaesthesia applied to a wide range of surgical operations is fitting justification for passing on the knowledge he has acquired.

Technical details are well presented in a style which, if a little unconventional, is refreshing and lucid. There are numerous illustrations which are clear although sometimes rather small, and they are original, a welcome novelty in a work of this kind.

To the practising surgeon wherever he may be this volume can be highly commended as a trustworthy guide but he will have to watch that his anaesthetist does not "borrow" it.

*Obstetrics and Gynaecology: A Synoptic Guide to Treatment.* By BEATRICE M. WILMOTT DOBBIE, M.A., M.B., F.R.C.S., D.M.R.E. Pp. xii+358, with 22 illustrations. London: H. K. Lewis & Co. Ltd. 1948. Price 20s. net.

This book is written primarily for young general practitioners to help them in their practice of domiciliary midwifery and in the treatment of gynaecological patients. The author has obviously first-hand knowledge of the practice of these branches of medicine in the home as well as the hospital and the double viewpoint has produced an understanding of the special problems and pitfalls with which the family doctor can be faced and an appreciation of the patient's questionings and anxieties. It is the expression of the experience acquired on these two features of practice that makes this volume different from the usual technical scientific textbook. The efficient management of common problems in the widest sense, environmental, technical and psychological, is considered.

As stated by the author diagnosis is only touched on, but as rational treatment can only follow correct diagnosis one feels the difficulties and common failings in this department might with benefit be enlarged on in a second edition.

*Atlas of Cardiovascular Diseases.* By I. J. TREIGER. Pp. 180, with 69 plates. London: Henry Kimpton. 1947. Price 50s. net.

As indicated by the title, the most important feature of this book is the illustrations, grouped into 69 plates, some of which are in colour. Each plate consists of several figures, comprising radiograms, electrocardiograms and autopsy specimens from a case of cardiovascular disease. A summary of the clinical history and signs, with a commentary, is printed on the facing page. The cases have been chosen to illustrate the main varieties of heart disease, and are grouped in appropriate sections, prefaced by a short section on the normal heart. In general the plates are of excellent quality though some of the coloured figures are disappointing. Short explanatory or introductory passages of text link the sections together.

Text and plates alike are printed on heavy glazed paper of a type that is rare in post-war Britain, and with the large print, wide spacing and generous margins, recall less austere days.

It is difficult to understand exactly for whom the book is intended. Much of the matter is elementary, suited to the needs if not the purse of the third year student. For the graduate, all the matter here presented is already available in much fuller form in the standard texts on cardiology.

## NEW EDITIONS

*Clinical Toxicology.* By CLINTON H. THIENES, M.D., PH.D., and THOMAS J. HALEY, PH.D. Second Edition. Pp. 373. London: Henry Kimpton. 1948. Price 22s. 6d. net.

This is primarily a textbook of toxicology and no attempt is made to discuss the chemistry or pharmacology of the poisons. A section on symptom diagnosis is included and should prove of great value in enabling the offending poison to be speedily recognised. Treatment, discussed from the pharmacological and pathological aspects is presented as simply as possible thus enabling the physician to deal adequately with whatever case of poisoning is encountered.

*Modern Clinical Psychiatry.* By ARTHUR P. NOYES, M.D. Third Edition. Pp. 525. Philadelphia and London: W. B. Saunders Company. 1948. Price 30s. net.

In this edition three new chapters dealing with psychotherapy, shock, and physical therapeutics, and child psychiatry have been incorporated. Those chapters increase the value and scope of this edition considerably. The book has always been an excellent one because the clinical descriptions are so good. From every point of view it can be recommended as a suitable textbook either for students or post-graduates.

*Pharmacology, Therapeutics and Prescription Writing.* By WALTER ARTHUR BASTEDO, PH.G., PH.M., M.D., SC.D. (HON.), F.A.C.P. Fifth Edition. Pp. x+840, with 82 figures. London: W. B. Saunders Company. 1947. Price 42s.

This edition has been completely re-written in order to bring it up to date. The book is divided into three parts. The first section of 44 pages is introductory and discusses the constituents of organic drugs, pharmaceutical preparations and methods of administration. Part II is the main body of the book and considers individual remedies and describes their pharmacological actions and therapeutic applications. Accounts are given of all U.S.P. preparations and of unofficial remedies of proved worth. Among the newer remedies considered may be mentioned amino-acids, B.A.L., demerol (pethidine) and streptomycin. The book has been written primarily as a guide to the physician in the treatment of his patients and on the whole fulfils this purpose admirably. In places, however, as for example in the section on anti-coagulants, the information given on therapeutic application is scarcely full enough to be really helpful or safe. The short third part on prescription writing could be omitted without loss from such an excellent book on pharmacology and therapeutics.

*A Practical Manual of Diseases of the Chest.* By MAURICE DAVIDSON, M.A., M.D., F.R.C.P. Third Edition. Pp. xvi+670, with 268 illustrations. London: Oxford University Press. 1948. Price 50s. net.

This edition contains several new chapters dealing with cysts of the lung and pleura and sarcoidosis. Many of the other chapters have been entirely re-cast while the remainder have all been brought up to date. The interval between preparing the manuscript and publication explains the absence of any reference to streptomycin. Although some individuals have a tendency to overstress the value of X-rays in the diagnosis of pulmonary disease Dr Davidson maintains a just balance between the clinical findings and the X-ray evidence. The book is liberally illustrated with X-rays but they do not dominate the text. This is a practical manual designed for clinicians and it is gratifying to find so much attention devoted to ætiology and pathology, without which a true appreciation of such diseases as pulmonary tuberculosis cannot be formed. The industrial diseases receive a fair allocation of space and when the reader wants to pursue the subject further he will find an ample bibliography, as is also the case at the end of each chapter. This is a comprehensive and well-illustrated volume on diseases of the respiratory system.

# BOOKS RECEIVED

- ANDRUS, WILLIAM DEWITT, Chairman, Editorial Board. *Advances in Surgery. Volume I.* (*Interscience Publishers, New York and London*) 66s.
- BAILEY, HAMILTON, F.R.C.S. (ENG.), F.A.C.S., F.I.S.C., F.R.S.E., and LOVE, R. J. MCNEILL, M.S. (LOND.), F.R.C.S. (ENG.), F.A.C.S., F.I.C.S. *A Short Practice of Surgery. Part V. Eighth Edition.* (*H. K. Lewis & Co. Ltd., London*). £2, 12s. 6d. set of Five Parts
- BEHRENDT, H., M.D. *Diagnostic Tests for Infants and Children.* (*Interscience Publishers, New York and London*) 45s.
- BERTWISTLE, A. P., M.B., CH.B., F.R.C.S.ED. *A Descriptive Atlas of Radiographs. Seventh Edition.* (*Henry Kimpton, London*) 50s. net.
- BOAS, ERNST P., M.D., and BOAS, NORMAN F., M.D. *Coronary Artery Disease.* (*The Year Book Publishers Inc., Chicago*) 33s. net.
- Revised and Edited by BRASH, JAMES COUPER, M.C., M.A., M.D., F.R.C.S.ED., F.R.S.E. *Cunningham's Manual of Practical Anatomy. Vol. III. Head and Neck: Brain. Eleventh Edition* (*Oxford University Press, London*) 21s. net.
- BROWNELL, K. O., R.N., B.S. *A Text-book of Practical Nursing. Third Edition.* (*W. B. Saunders Company, London*) 19s.
- BURCH, GEORGE E., M.D., F.A.C.P., and WINSOR, TRAVIS, M.D., F.A.C.P. *A Primer of Electrocardiography. Second Edition* (*Henry Kimpton, London*) 22s. 6d. net.
- DAS, K., M.B. (CAL.), F.R.C.S. (ENG. AND EDIN.). *Clinical Methods in Surgery. Second Edition.* (*The City Book Company, Calcutta*) 35s. net.
- DUKE-ELDER, Sir W. STEWART, K.C.V.O., M.A., D.SC. (ST AND.), PH.D. (LOND.), M.D., CH.B., F.R.C.S., HON. D.SC. (NORTH-WESTERN). *Text-book of Ophthalmology. Volume IV.* (*Henry Kimpton, London*) 70s. net.
- FINE, JACOB, M.D. *Care of the Surgical Patient.* (*W. B. Saunders Company, London*) 40s.
- HILL, CHARLES, M.A., M.D., D.P.H., and WOODCOCK, JOHN. *The National Health Service.* (*Christopher Johnson, London*) 16s. net.
- HILL, H., F.R.SAN.I., F.S.I.A., A.M.I.S.E., and DODSWORTH, F., M.R.SAN.I., M.S.I.A. *Food Inspection Notes. Third Edition* (*H. K. Lewis & Co. Ltd., London*) 7s. 6d. net.
- HOARE, EDWARD D., M.D. *The Sulphonamides in General Practice.* (*Staples Press Ltd., London*) 5s. net.
- HUTCHISON, Sir ROBERT, Bart., M.D., F.R.C.P., and HUNTER, DONALD, M.D., F.R.C.P. *Clinical Methods. Twelfth Edition* (*Cassell & Co. Ltd., London*) 17s. 6d. net.
- International Congress on Mental Health, London, 1948. *Volume I. History, Development and Organisation.* (*H. K. Lewis & Co. Ltd., London*) 10s. net.
- International Congress on Mental Health, London, 1948. *Volume II. Proceedings of the International Conference on Child Psychiatry, 11th-14th August.* (*H. K. Lewis & Co. Ltd., London*) 10s. net.
- International Congress on Mental Health, London, 1948. *Volume III. Proceedings of the International Conference on Medical Psychotherapy, 11th-14th August.* (*H. K. Lewis & Co. Ltd., London*) 10s. net.
- International Congress on Mental Health, London, 1948. *Volume IV. Proceedings of the International Conference on Mental Hygiene, 16th-21st August.* (*H. K. Lewis & Co. Ltd., London*) 20s. net.
- JAMIESON, ELIZABETH M., B.A., R.N., and SEWALL, MARY F., B.S., R.N. *Trends in Nursing History. Third Edition* (*W. B. Saunders Company, London*) 22s. 6d.
- LEVINE, SAMUEL A., M.D., and HARVEY, W. PROCTOR, M.D. *Clinical Auscultation of the Heart.* (*W. B. Saunders Company, London*) 32s. 6d.
- LICHTMAN, S. S., M.D., F.A.C.P. *Diseases of the Liver, Gall-bladder and Bile Ducts. Second Edition.* (*Henry Kimpton, London*) 90s. net.
- MACALPINE, JAS. B., D.SC., F.R.C.S. *Cystoscopy and Urography. Third Edition.* (*John Wright & Sons Ltd., London*) 63s.
- MCLESTER, JAMES S., M.D. *Nutrition and Diet in Health and Disease. Fifth Edition.* (*W. B. Saunders Company, London*) 45s.
- McMURRAY, T. P., C.B.E., M.B., M.CH., F.R.C.S. (EDIN.). *A Practice of Orthopaedic Surgery. Third Edition.* (*Edward Arnold & Co., London*) 30s. net.
- MEDVEI, V. C., M.D., M.R.C.P. *The Mental and Physical Effects of Pain.* (*E. & S. Livingstone Ltd., Edinburgh*) 3s. net.
- PRICE, ALICE L., B.S., R.N. *The American Nurses Dictionary.* (*W. B. Saunders Company, London*) 19s.
- STEVENSON, R. SCOTT, M.D., F.R.C.S.ED., and GUTHRIE, DOUGLAS, M.D., F.R.C.S.ED. *A History of Oto-Laryngology.* (*E. & S. Livingstone Ltd., Edinburgh*) 17s. 6d. net.
- Edited by STIEGLITZ, EDWARD J., M.S., M.D., F.A.C.P. *Geriatric Medicine. Second Edition.* (*W. B. Saunders Company, London*) 60s.
- THOMA, KURT H., D.M.D., F.D.S.R.C.S. (ENG.). *Oral and Dental Diagnosis. Third Edition.* (*W. B. Saunders Company, London*) 47s. 6d.
- WIDDESS, J. D. H., M.A. (DUBLIN), L.R.C.P. & S.I. *An Account of the Schools of Surgery, Royal College of Surgeons, Dublin, 1789-1948.* (*E. & S. Livingstone Ltd., Edinburgh*) 17s. 6d. net.

# ACUTE INFECTIONS OF THE HAND

By T. I. WILSON, M.B., F.R.C.S.Ed.

IT has been stated by some that in this "Antibiotic Age," the use of the surgeon's knife is an anachronism in the treatment of acute infections of the hand. Many of us, however, feel that this is an expression of unusual optimism rather than a statement of fact.

This is a matter on which we, the staff of the Surgical Out-Patient Department of the Royal Infirmary of Edinburgh, have certain definite views and I speak to-night on behalf of that staff in support of the treatment which, at present, we adopt in these cases.

I must here acknowledge my debt to my colleagues in the department

## The Transactions of the Medico-Chirurgical Society of Edinburgh

SESSION CXXVIII.—1948-1949

CLINIC OF PROFESSOR FUCHER and his junior colleagues at University College Hospital. I have chosen this report as representative of the views of the more conservative school because the treatment which they adopt in their clinic differs from ours only in that they delay incision in *all* cases until pus formation is evident. In all other respects their principles of treatment are essentially the same as those which we adopt in the Surgical Out-Patient Department of the Royal Infirmary.

I propose to draw a few parallels which may perhaps be sufficiently provocative to form a basis for discussion to-night.

The principles of the treatment which we at present adopt in these painful and damaging lesions are three in number.

*First.*—The provision of adequate rest.

This is the most important therapeutic agent which we possess to-day and is probably the most frequently neglected even though it

Read at a Meeting of the Medico-Chirurgical Society of Edinburgh on 1st December 1948.

was instituted immediately after the Creation and has been repeatedly emphasised down through the ages, by the great Hippocrates himself and by such eminent clinicians as William Shakespeare, John Hilton and the eminent Edinburgh surgeon whose dictum was "A House Surgeon's efficiency is directly proportional to the number of signatures in the Morphine Book."

*Second.*—The provision of an adequate supply of anti-bacterial influence where it is most required.

*Third.*—The performance of timely and adequate incision where required.

It is in the application of this third principle that our practice is at variance with that of the conservative group of surgeons.

Before we advance further, there are various basic factors which we must first consider. I hope you will bear with me while I recall these briefly.

Firstly we must consider the *anatomy* of the hand with reference to the sites of infection.

The integument of the hand is sensitive and of varying texture. Infections of the skin may be subcuticular or intracutaneous. These may be seen in the infected blisters between the webs, over the finger pulp from superficial punctures, and around the nail fold as a paronychia and onychia.

Underlying the skin is the subcutaneous fatty tissues in which subcutaneous infection, a cellulitis, may occur as a result of punctures or by spread from other areas.

In this connection, may I remind you of the special importance of the subcutaneous tissue of the finger pulp, which is divided into separate compartments by non-extensile septa running longitudinally between the periosteum of the distal phalanx and the skin.

We must remember the relation of the distal phalanx and its blood supply in the finger pulp. The digital arteries run distally through the pulp tissue close to the antero-lateral surface of the phalanx to reach the nutrient foramina of the phalanx which enter the diaphysis in its distal third; whereas the branch of the digital artery supplying the epiphyseal or juxta-articular portion of the phalanx lies proximal to the compartmented pulp.

Be it noted that it is the importance of these anatomical facts (not the facts themselves) which is denied by many of the protagonists of ultra-conservative treatment in finger pulp infections.

Infection of the diaphysis of this distal phalanx is all too common and may even result in sequestration.

Infections may occur in the flexor tendon sheath, to the detriment and possible destruction of the contained tendons of flexor digitorum sublimis and profundus. These tendons depend for their slender blood supply on small vessels in the vincula brevia (distally) and vincula longa (proximally). It is well to remember how close these sheaths

are to the skin at the interphalangeal flexures and how thin the sheaths are at these points.

The extent of the digital flexor sheaths is of great importance. The sheaths of the thumb and fifth digit extend proximally to the wrist as the radial and ulnar bursæ, by which routes infections may reach the quadratus space (Parona) in the forearm, whereas the sheaths of the index, middle and ring fingers terminate in ampullæ a short distance distal to the distal palmar crease.

We should recall, too, that the two outer bursæ communicate over the carpus in a high proportion of cases.

We must also remember that all the digital sheaths are double coated. There is the outer fibrous sheath, thick over the phalanges and thin at the flexures, and there is also the inner serous sheath.

The fibrous sheath is a rigid layer and terminates at the base of the finger, enclosing nearly the whole of the digital serous sheath. No such fibrous sheath covers the radial and ulnar bursæ so that any necessary expansion is thereby unimpeded.

We must also remember the thenar and middle palmar spaces whose boundaries are well known. We should recall, however, that spread of infection to these spaces may be the result of subcutaneous infection of the digits, or web infections, spreading along the so-called lumbrical canals to the corresponding space.

One other fact we would do well to remember is that abscesses of intracutaneous and subcutaneous spaces may be of the "collar-stud" type—a small track in the floor of the superficial abscess communicating with a deeper suppurating cavity.

*Bacteriologically* these infections are nearly always the penicillin-sensitive staphylococcus aureus or a streptococcus. We have not in our series of cases specifically identified the organisms, nor have we carried out sensitivity assay. These investigations have not been considered practicable although it is admitted that such information would be valuable for record purposes.

The *pathology* of these lesions is simply the pathology of acute inflammation of pyogenic organismal origin, modified by the various anatomical considerations with which we have already dealt.

There are the usual hyperæmia, œdema and pain of the spreading stage followed most frequently by localisation and the suppuration with which we are all so unfortunately familiar.

This pathological process runs a course which is influenced by certain factors—the anatomy of the site, the virulence of the organism, the sufferer's general health and resistance, and the propriety of the treatment adopted. This last factor is one which requires full co-operation by the patient.

A further factor which we believe to be of paramount importance is *tension*. This entity is probably the surgeon's worst enemy in his



practice, and has a profound effect on the course of the pathology of acute infections of the hand.

It is well known that infection under tension will force its way out of its confined space by whatever route it may find. It is this fact which we believe to be responsible for the serious consequences which are far too often met with in such infections as those of the finger pulp and the flexor tendon sheaths of the digits.

As we all know, infection of the finger pulp is frequently complicated by infection of the distal phalanx of the finger. This osteitis may be followed by sequestration of part or even the whole of the diaphysis of the bone resulting in gross permanent deformity of the finger pulp after a prolonged period of disability.

It is our opinion that this unfortunate state of affairs is not the result of ischæmic necrosis of the bone—proof of this is certainly lacking—but is due to an actual infection of the bone by organismal invasion along the nutrient foramina, which are in the distal third of the diaphysis of the phalanx. It should be noted that the radiological signs of bone damage are always first seen in this distal third.

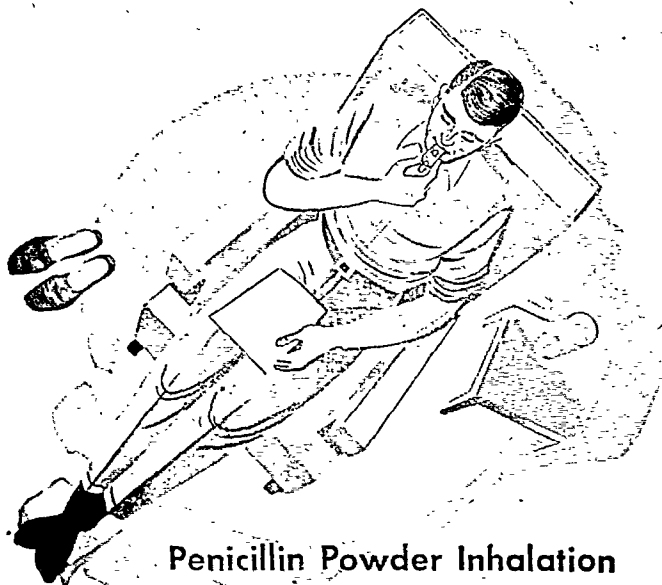
In young fingers the epiphysis is spared as its nutrient foramina lie proximally, outwith the confined space of the pulp. We must also remember that it is rare indeed to meet with osteitis of either the middle or proximal phalanx in cellulitis of the more proximal portion of the finger.

It is for these reasons that we believe that tension within the finger pulp is responsible for this infection and destruction of the phalanx. We therefore continue to act accordingly and relieve the tension in the pulp by early incision even in the stage of cellulitis.

This distal phalanx is the bone of contention which we have to pick in the present argument regarding the treatment of infected hands.

Tension also plays a sinister rôle in cases of suppurative tenosynovitis. The blood supply of the tendons is slender and delicate and the raised tension within the sheath may thrombose and invade these vessels thereby gaining entry to the tendons along their paths with resultant infection and death of the tendon. This same infection in the sheath, if under tension, invades and destroys the endothelium of the serous sheath, with resultant fibrosis and fixation of all the structures involved, leaving a fixed, deformed and useless digit. This finger may be such a nuisance to its owner that amputation may be the outcome.

It is interesting to note the differing results in these cases. Infections of the sheaths of the index, middle and ring fingers are all too seldom devoid of serious consequences for the finger concerned, whereas a much more satisfactory result follows successful treatment of infection in the sheaths of the thumb and fifth digit. We believe that this difference is due to the fact that tension within the sheaths of the index,



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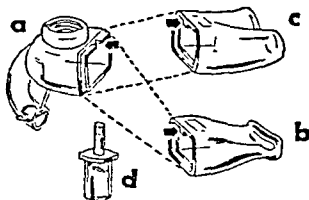
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middle and ring fingers is confined within the non-extensile fibrous sheath, whereas in the case of the thumb and fifth finger, the tension is relieved by expansion of the radial and ulnar bursæ. It is the experience of most surgeons that the prognosis is best when the infected sheath is that of the fifth finger.

One further effect of tension which we believe to be of importance is its interference with the access to the infected area of any anti-bacterial agent which we may employ systemically. We believe that when tension is present in the finger pulp, theca, or any other cavity, the penicillin we employ cannot be adequately conveyed thereto by an obstructed circulation.

It is upon these facts and interpretations that we plan our treatment.

Over 1000 cases of acute infection of the hand were dealt with in the Surgical Out-Patient Department of the Royal Infirmary in 1947. I make no attempt to-night to produce figures of the number of infected hands seen prior to the comparatively recent era of penicillin but it is our opinion that acute infections of the hand are less common in hospital practice than was formerly the case, and are less virulent in type.

While the principles of treatment to which we have adhered for the last few years have not altered in any great measure, certain modifications have been made from time to time. One important modification was made in August of this year, and in consequence of this fact I propose to discuss briefly two groups of our cases.

Each group covers a two-month period before and after the date mentioned. The first period was taken at random from the records of 1947 and is hereafter designated Group I. The second two-month period comprises the first eight weeks after the recent modification was made in August of this year.

While we are fully aware that this method of presentation markedly reduces the numbers available, we feel that each period contains a number which is adequate to provide food for thought this evening.

The change in our treatment which we introduced this August was designed to secure a more adequate dosage of penicillin in our cases, and to this end we increased our standard dose from 100,000 units twice per day to 500,000 units twice daily. In addition, to ensure that our patients duly received their doses regularly we now ask those who live within reach to report at the department in the morning and in the evening for the administration of their penicillin.

In Group I, therefore, we recommended 100,000 units of penicillin twice a day and returned the patient to his own doctor for its administration. In Group II we gave five times the dose and administered it ourselves in all "city" cases.

Our reasons for making the change were three in number: first, we felt that a dose of 100,000 units in twelve hours was inadequate; secondly, we so often found that, for a variety of reasons patients failed

to obtain their dose regularly and sometimes did not receive some at all; thirdly, by seeing patients twice in the day, the lesion could be more closely observed and the optimum opportunity taken for incision where necessary.

Table I shows the numbers of cases comprising our two groups. These are classified according to the major lesion present. The smaller figures give the percentages of the total number of cases in the group. I have here contrasted the combined figures of our two groups with the analysis of the series which I have already mentioned published by the Clinic at University College Hospital. We see that there were 196 cases in Group I and 177 cases in Group II. The

TABLE I

		Group I.	Group II.	Combined Groups.	U.C.H.
Pulp . . .	Number	40	50	90	80
	Percentage	20.4	28.2	24.1	21.2
Cellulitis . .	Number	66	47	113	115
	Percentage	33.6	26.6	30.3	30.6
Paronychia . .	Number	54	49	103	83
	Percentage	27.6	27.7	27.6	22.1
Web . . .	Number	25	22	47	13
	Percentage	12.8	12.4	12.6	3.4
Theca . . .	Number	6	...	6	3
	Percentage	3.1	...	1.6	0.9
Palmar space .	Number	4	2	6	82
	Percentage	2.0	1.1	1.6	
Others . . .	Number	1	7	8	21.8
	Percentage	0.5	4.0	2.2	
Total . . . . .		196	177	373	376

combined total of four months work is only three short of the total number of cases reported by University College Hospital covering a period of eighteen months.

It is interesting to note how constant are the frequencies of the commoner lesions. There are, of course, certain discrepancies between our figures and those published by University College Hospital. These are most noticeable in the cases of web infections and in the last miscellaneous group.

This, it would appear, is largely due to a difference in terminology. For example, some of our web infections would be classed as subcutaneous or subcuticular infections at University College Hospital. I think, however, that we can consider the two series comparable in their more important characteristics.

We make no claim that each case has been treated invariably according to the complete set of rules laid down. Each infected hand must be dealt with in the manner most suited to its owner's best interests, and many minor factors—other than those we have already mentioned—must be taken into account. Patients receive treatment at the hands of different members of the staff and occasionally unorthodox and even archaic methods have been found to occur, perpetrated possibly by the less enlightened or by those to whom the methods of yesterday are still their pride.

In general, however, rest is applied by splinting the part. Plaster of Paris slabs are used for the purpose and the arm is placed in a sling. In out-patient practice it is not possible to ensure "general" rest to the whole patient and "faut de mieux" we must be content with local rest to the hand.

*Penicillin* is the antibacterial agent we employ and is now given in two doses in twenty-four hours. Each dose consists of 500,000 units. The drug is administered intramuscularly as we believe that the most satisfactory method of bringing penicillin and organisms together is through the medium of the blood stream. The drug is used in all cases prior to the formation of pus. If and when pus forms its use may be continued if deemed necessary or it may be considered unwise if much slough is present, as continued penicillin in such circumstances has been found to delay separation of these sloughs.

*Incision* is required in all cases in which pus has formed. The abscess is incised where it is found most appropriate. The subcuticular whitlow has its roof removed, the web abscess is opened where it points, the paronychia is evacuated by elevation of the nail fold right to the root of the nail, the subungual collection of pus is drained by the removal of that portion of the nail which overlies it. In all cases space for drainage must be provided. It may be that simple linear incision is sufficient, but frequently it is necessary to excise a narrow ellipse or small circle of skin so that premature closure does not take place. In general, drains are not used and if they are considered necessary are removed after minimal periods. Care must be taken that the deeper cavities of "collar-stud" abscesses are adequately opened.

In addition to these obvious indications for incisions we use incisions to relieve tension in certain cases. Of these instances the most notable is the acute infection of the finger pulp—the simple "felon." It is in this respect that our only major difference of opinion with the protagonists of ultra-conservatism lies. We believe that tension must be relieved for the reasons I have already stated. Not least of these reasons is the humanitarian one. Those of us who have experienced acute pyogenic infection in an enclosed space realise the misery it produces. Furthermore, it is our experience that pus can be present in a finger pulp after only one sleepless night of throbbing pain. It is,

therefore, our practice to relieve this tension whenever we consider it necessary and the examining finger can readily detect dangerous tension in the finger pulp.

This relief incision is performed unilaterally. The knife is entered  $\frac{1}{4}$ " distal to the distal interphalangeal crease, passing through the pulp to, but not through, the skin on the opposite side. The knife point is then swept distally to open all interseptal spaces. Not infrequently we find that suppuration has already commenced and in such cases counter incision may then be necessary.

After incision tulle gras or dry dressings are applied and splintage is resumed.

With regard to subsequent treatment after incisions, dry dressings are the most satisfactory. Wet dressings are deprecated on account of the fact that they lead to maceration of the skin. Dressings of the "fomentation" variety are seldom if ever applied deliberately, but

TABLE II

Infection.		Group I.	Group II.	U.C.H.
Pulp . . . .	Number Days	40 25.5	50 15.4	80 16.8
Cellulitis . . . .	Number Days	66 14.4	47 18.0	115 15.2
Paronychia . . . .	Number Days	54 18.8	49 12.2	83 9.8
Web . . . .	Number Days	25 14.2	22 12.2	13 13.6

kaolin is sometimes employed in those few cases where a brawny induration is slow in resolving.

Vaseline dressings—applied as "tulle gras" are more comfortable from the patient's point of view, but as vaseline inhibits, or at any rate delays epithelialisation, these vaseline—or oily dressings of any kind—should not be employed in the healing stage. Redressing is carried out as infrequently as possible.

Table II shows the average periods—in days—during which our commonest classes of infection required treatment. We note that in the cases of finger pulp infection, paronychia and web infections, our improved treatment would appear to have resulted in a shortening of the period of treatment.

Only in cases of cellulitis is the average period longer in Group II than in Group I. This is unfortunately due to two patients, one who refused penicillin as he knew he was sensitive thereto and a second patient whose infected hand showed gross sloughs which were long in separating—partly, I fear, due to the continued use of penicillin. Both these cases took many weeks to heal.

With the possible exception of the healing period in cases of paronychia our cases are comparable with those reported by University College Hospital.

Table III analyses in greater detail the cases of finger pulp infections. Here I think some significant figures appear. It will be seen here that the results in our two groups compare favourably with those treated conservatively. The duration of treatment is, as we have already seen, comparable with column 3. The average duration of total disability compares favourably with column 3. In these two sets of figures we find that the effect of our increased dosage of penicillin is manifest.

When we come to consider the complications which arise in these infections we cannot but feel that the value of early incision is, if not demonstrated, at least suggested. We find that the increased dosage of penicillin has not influenced the complication rate, nor has it reduced the frequency of the commonest of these complications—phalangeal

TABLE III

Finger Pulp.	Group I.	Group II.	U.C.H.
Number of cases . . . . .	40	50	80
Average period from onset to treatment	6.0	5.5	5.8
Average duration of total disability .	31.5	19.7	23.7
Number of cases complicated . . . .	5	7	19
Percentage complicated . . . . .	12.5	14	24
Phalangeal osteitis . . . . .	4	5	16
Percentage osteitis . . . . .	10	10	20

osteitis. In both our groups, however, the rate of complication and the frequency of osteitis is approximately half that reported in the series where relief incision is specifically condemned.

It is of interest to note that all of our cases of finger pulp infection which have shown osteitis of the phalanx have either come to treatment—*i.e.* relief incision—late or have been incised in a manner which has failed to relieve the tension within the pulp. We frequently find that such cases have already been incised on the volar aspect of the pulp—such incision only opening one compartment. The four cases in Group I averaged eight days between onset and the institution of our treatment. Two of them had been unsatisfactorily incised. In Group II the five cases of osteitis averaged 11.5 days between onset and arrival in the department. Three of these had been incised inadequately. We note that these figures indicate a rather longer period prior to institution of treatment than the relative figures for the whole number of cases of pulp infection in each group. Thus our deduction is that the causes of phalangeal infection would appear to be (1) delay in commencing treatment—*i.e.* relief incision—and (2) inadequate relief incision.



If and when phalangeal infection does occur no change in treatment is indicated. The same method which we have adopted in soft tissue infection will also deal with bony infection. If infection and sequestration take place we find that some sequestra will be absorbed and good healing of the phalanx and pulp follow. We are of the opinion that operative removal of small sequestra is unwise—as it is either followed by the separation of more sequestra or the finger pulp is grossly flattened and permanently deformed—often leaving a painful hard pulp remnant for which amputation may be the only relief. Larger sequestra may require operative assistance in their extrusion—but such removal should be delayed until separation is complete in order to avoid unnecessary damage to the remains of the pulp. The healing time in cases of phalangeal infection is, of course, protracted, and the total period of disability suffered by the unfortunate owner of an infected phalanx is considerably greater than that of his fellow-patient whose bone escapes.

The average period of disability in the 4 cases of osteitis in Group I was ninety-three days and in the 5 cases in Group II was forty-two days.

We cannot offer an analysis of the results in infections of the tendon sheaths. The number of cases in Group I is too small to be of statistical value. The 6 cases seen were not all treated to a conclusion in the department and it is our practice to refer such to the wards. We have gained certain impressions regarding these lesions—but impressions are inadmissible this evening.

There are many difficulties to be overcome in the treatment of acute infections of the hand and not least of these is the impossibility of satisfactory control of the patient when he is treated as an out-patient. It is probably only by admission to hospital that such adequate control will be obtained and his treatment be maintained at an adequately high level so that the present disastrously high rate of permanent disability and disfigurement may be reduced.

Meantime, to all surgeons who may be called upon to treat acute infections of the hand (particularly those of the finger pulp), we would offer the gratuitous advice given to Francis Mitchell Caird when the Vice-Chancellor of the University was over tiresome in conferring upon him his honorary degree—"Tak a knife tae him Cairdie."

#### DISCUSSION

*Mr Quarry Wood* said that the Society were very grateful to Mr Wilson and to the Council for focusing their attention on this very important subject. He was able to make a small contribution to the discussion owing to his having been in charge of the surgical ailments of the nurses in the Royal Infirmary for some years. These nurses formed a special group of cases since their infections were usually reported early and the treatment was under careful supervision. Dr Verney's records showed that from 1941 to

1948 there had been 405 cases of infected hands ; of these 310 were treated as in-patients in the sick-room. The types of infection to which nurses are most liable are the pulp infection over the terminal phalanx and infection at the nail fold. The pulp infections were treated at first with sulphonamides ; later, when penicillin became available, they were given penicillin in the more severe cases, sometimes alone, but usually in combination with sulphathiazole or sulphadiazine. Operative treatment was given up except for pricking a residual purulent blister. Infection at the nail fold was treated by tucking in sulphanilamide powder with the blunt end of a needle ; in some cases it was necessary to incise a small collection of pus or to cut away the edge of the nail before this could be properly done. In 405 cases there had been no case of necrosis of bone or any other complication and all the cases had made complete recoveries without any kind of disability.

The drawbacks to incisions were, firstly, that they are nearly always unnecessary now that effective chemotherapy is available, they may leave the patient with a sensitive scar, they permit the entrance from the skin of other organisms which are frequently insensitive to penicillin, and in some cases they even appear to break down the protective barrier which nature has established and to spread the infection.

Mr Wood stated that the more severe cases of hand infections are now uncommon. In 1946 and 1947 only seven cases were admitted to his wards. They included palmar space infections, severe lymphangitis, and one case of infection of the sheath of the flexor pollicis longus. All the cases were treated conservatively with penicillin. Only one case was operated on ; in this case a residual abscess was incised. All the cases made excellent recoveries with one exception ; in this case infection of the flexor pollicis longus sheath had been present for four weeks before admission and the tendon had already sloughed.

The analogy between acute osteomyelitis and infections of the hand was pointed out, the infecting organisms being similar in the two cases. A paper by Twistington Higgins and Browne on 31 cases of acute osteomyelitis treated with penicillin and without operation was very impressive. If pus formed outside the bone, the pus was aspirated and penicillin injected into the abscess cavity. There were no deaths in the series and all the cases made perfect recoveries with one exception, in which a flare-up took place after an incomplete course of penicillin. The speaker had had similar results in a small number of cases of acute osteomyelitis and acute infective arthritis. Mammary abscesses would clear up under treatment with penicillin alone, and carbuncles, however large, responded extremely well and did not require operation. If such massive infections responded to conservative treatment, it seemed likely that similar results would be obtained in the more limited infections in the hand. In conclusion, Mr Wood emphasised again that the group of nurses mentioned were early cases and under specially favourable conditions for conservative treatment.

*Mr T. McW. Millar* said he was much interested in the presentation of the subject. Infection of the hand was of course a very serious thing. In a recent paper on the subject it was estimated that perhaps less than 1000 cases—the number going through the S.O.P.D. annually—meant something like six months loss of work for 100 men, and that was a very serious matter.

There were two entirely different methods of treatment—the conservative one quoted by Mr Wilson and supported by Mr Wood, and the traditional method of incision plus rest and the use of antibiotics. Mr Millar felt it was dangerous to draw conclusions from Mr Wood's series. Mr Wood had not mentioned how long the infection had been present in his cases before they reported for treatment. Mr Wilson had shown that in his series of pulp infections the condition had been present for five or six days before treatment—he was sure Mr Wood's cases had been seen at a much earlier period.

Another point Mr Wood had omitted to mention—how much immobilisation had been used. That was an important factor. Mr Wood had treated his cases with sulphonamides—Mr Millar doubted very much whether, as staphylococcus aureus is relatively insensitive to these drugs, much benefit could come from it—most of the benefit was probably the result of rest.

Mention had been made by Mr Wood of the treatment of paronychia—Mr Millar's experience was that incision was necessary unless the case was treated in the early stage. Nothing had been said about tendon sheath cases, but they were relatively uncommon.

One or two points Mr Millar wished to ask Mr Wilson—what form of penicillin did he use for intramuscular injection? Was it the ordinary watery solution or a solution in oil? Mr Wilson had not mentioned anaesthesia—did he agree that a general anaesthetic should be used?

Finally, Mr Millar drew the attention of the meeting to a recent paper from Oxford by Loudon, Miniers and Scott (1948).<sup>\*</sup> Here a third method was advocated and the results claimed were the best Mr Millar had yet seen. The method used was incision, preferably using flaps, exposure of the part, excision of necrotic tissues, primary suture of the wound and immobilisation, the patient being given intramuscular penicillin.

Mr Wilson had quoted his period of healing in pulp space infections as 15.46 days; the U.C.H. series as 16.8 days; the Oxford workers claimed 11.8 days. Other figures were:—Web infection (Oxford called it distal palm infection)—Mr Wilson's 12.2 days; U.C.H. 13.6 days; Oxford 9 days.

The Oxford claims, if confirmed, indicated a distinct advance in the treatment of infections of the hand.

*Dr Verney* referred to the difference between the series of cases presented by Mr Wilson, and those presented by Mr Wood: the average duration of symptoms in Mr Wood's cases being not longer than 24 hours, whilst those of Mr Wilson averaged 6 days. Nurses are urged to report at once the earliest manifestation of septic infection of the fingers: consequently the majority of cases were treated efficiently from the earliest stages. There were, however, a large number of advanced and grossly infected hands, which had arisen from concealment of the symptoms. These severe cases were comparable to the cases described by Mr Wilson, yet they responded very satisfactorily to the conservative method of treatment. *Dr Verney* reaffirmed that the 405 cases treated conservatively by chemotherapy, without recourse to surgical intervention until the infection was completely localised, all recovered rapidly: and that there had been no cases of serious septicæmia, bone necrosis or ultimate loss of function or disfigurement of the hands in any instance.

<sup>\*</sup> Loudon, J. B., Miniers, J. D., and Scott, J. C. (1948), *Journal of Bone and Joint Surgery*, 30-B., 409.

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Mr Wilson had stated that the cause of osteitis was delay in incision, but in Dr Verney's opinion the real reason was delay in chemotherapy. There appeared to be no question that the secret of success in treating all septic infections of the hands was early diagnosis and immediate chemo-therapy.

Dr Verney disagreed with Mr Millar concerning the value of sulphonamides. He maintained that, combined with rest, they were most beneficial—although less efficient than penicillin. Of the 95 nurses treated as out-patients, many had been treated with sulphonamides and remained on duty. The average loss of time for the 310 nurses treated as in-patient was 11.8 days. This figure included the usual sick leave granted to each nurse after such an infection. The actual time of healing was considerably less.

The resistance of the patient to infection had been mentioned by Mr Wilson. There has been a popular belief that yeast is a valuable agent, both curatively and prophylactically, in the relief of staphylococcal infections of the skin. All nurses with septic fingers were given as a routine measure a concentrated yeast preparation—Valogen B.D.H. 1 dr. T.I.D. It was his impression that this measure had been of great benefit and, in consequence, he had arranged to increase the vitamin B content of each nurse's diet by the addition of one-sixth of an ounce of wheat germ daily.

*Mr R. L. Stewart* said that from his experience of the Out-Patient Department, he did not feel that the two types of patients were quite comparable—the nurses and the out-patients. The former had all the advantages of quick attention, whereas the latter had few of these advantages.

As one who had suffered both from paronychia and from pulp infection, Mr Stewart stressed the fact that the pain is severe and sometimes even morphia is required. As he had had his infections before the advent of penicillin, he could not say whether such therapy alone relieved pain.

One question he wished to ask Mr Wilson in regard to pulp infection. Mr Wilson had advised early incision—Mr Stewart wondered in how many, if any, cases where early incision had been carried out, had there been subsequent osteitis of the phalanx. If none had occurred, such surgical intervention must be looked upon as a really worth while procedure.

Mr Stewart agreed that adequate penicillin therapy had an extraordinary effect on cases admitted to the wards. Practically all cases of major hand infections thus treated as in-patients subside rapidly, while incisions have become the exception rather than the rule.

*Mr H. W. Porter*, in supporting Mr Wilson's views on treatment, stressed the need for early diagnosis and rest and emphasised the difference in the type of case met with in the S.O.P.D. and those which were seen among the Nursing Staff. He recalled several cases which had been referred for treatment after three weeks, these all required incision and he also mentioned several

cases which had gone on to pus formation in spite of the adequate administration of penicillin within the first 24 hours.

Mr Porter felt that it was very difficult to deal adequately with these cases as out-patients—they should all be admitted. He was of the opinion that more attention should be paid to the patient's general resistance, and was interested in Dr Verney's remarks about the treatment with yeast. He wondered if the incidence of infection had decreased among the Nursing Staff of the Infirmary since the introduction of a fuller diet two years ago.

With regard to the results from penicillin treatment, Mr Porter felt that many cases did not respond so dramatically as previously. Possibly more resistant strains are being encountered now. He thought it rather optimistic to state that the acute phase of all cases treated with penicillin would subside in 48 hours as he had recently had a case of thenar space infection in which the pyrexia and local symptoms had persisted for eight days in spite of adequate dosage.

Mr Porter was interested in Mr Millar's remarks about the early excision of all infected tissue and primary suture under adequate penicillin cover but foresaw great difficulty in deciding what was infected tissue in such a small structure as the pulp before a definite slough had formed.

*Dr Orr* asked Mr Wilson whether he would advise the use of a single injection of procaine penicillin in 24 hours as an alternative to two single doses of 500,000 units penicillin sodium. He also wondered if penicillin resistance rules out the use of penicillin therapy at a later date.

*Mr J. R. Cameron* spoke of the cases attending the out-patient department at Leith Hospital where many of the patients were referred for treatment when the infection had been present for several days, and operative treatment was frequently essential. He supported Mr Wilson's indications for, and use of the knife.

Mr Cameron maintained that penicillin in the treatment of the infected hand was as effective and potent as ever, the queue of patients for injections, instead of, for painful and protracted dressings was still dramatic.

Mr Cameron referred to 270 staphylococcal infections treated in the army in a heat-stroke area between July and October 1942, where the extreme heat and a vitamin-deficient diet were factors in the etiology. He referred to the reports of the Anglo-Iranian Oil Company whose staff at Abadan stressed the importance of a high vitamin dietary for prevention of such infections and he was particularly interested in Dr Verney's reference to diet and the use of yeast.

*Mr Jeffrey* questioned Mr Wilson's explanation of the pathogenesis of bone infection in pulp infections. According to Mr Wilson the position of entry of the nutrient artery allowed bacteria to gain easy access to the bone, and produced an osteitis. This was an interesting conception but at variance with the usual view, maintained by Kanavel and many others, that the bone necrosis is due to ischæmia—tension in the pulp obliterating the arteries.

Mr Jeffrey agreed that 12-hourly injections of penicillin was a convenient and satisfactory method of dosage in these hand infections, but thought that

100,000 units twice daily—rather than Mr Wilson's 500,000 units twice daily—should suffice. Mr Jeffrey said that he had treated 15 hand infections (pulp, space and sheath) with 20,000 units 3-hourly, and 15 with 100,000 units 12-hourly, and the results in the twice daily regime were every bit as good.

*The President (Sir Henry Wade)* thanked Mr Wilson for his address and commented on the present-day picture with chemotherapy compared with what happened previously, when finger infections were not infrequently followed by a rapidly spreading cellulitis, lymphangitis, septicæmia and death.

In reply, *Mr Wilson* said: I am most interested in the series of cases reported by Mr Quarry Wood and by Dr Verney. One cannot, however, but feel, that the two series are not really comparable and that the cases occurring among the Nursing Staff are seen early; whereas the cases seen in the Out-Patient Department reported for treatment much later. We too have our cases which abort with chemotherapy alone, but comparatively few of our cases are seen early enough for this form of treatment.

Sir Henry Wade mentioned lymphadenitis and lymphangitis which are, of course, seen in a proportion of our cases and I feel in those in which the streptococcus is to blame. These react extremely well to treatment with penicillin but we consider these cases a definite indication for admission, and from our point of view, are complications of secondary importance to the primary lesion.

In reply to Mr Millar I must say that the penicillin we employ is of course an aqueous solution of the sodium salt, and in all our operations for these lesions general anæsthesia is invariably employed, as we consider that local anæsthesia has no place in the treatment of acute infection of the hand. We employ a tourniquet where the infection is a deep one but do not use it in the treatment of superficial infection. I feel, with regard to his question concerning the Radcliffe papers where excision of these infective lesions is described, that such excision must surely still further increase the deformity and therefore the disability ensuing, particularly in infections of the finger pulp.

Mr Stewart has raised two most important points: firstly, he points out the excellence of the results obtained in lesions where the patient is admitted to the ward for treatment, due entirely I am sure to the care with which their treatment is supervised and the satisfactory control of the patient under such circumstances, a point also stressed by Mr Jeffrey. In reply to Mr Stewart's question regarding the numbers of phalangeal osteitis in cases early incised, all I can say at the moment is, that our cases of osteitis have occurred in those patients whose finger pulps were incised late or were inadequately incised.

Mr Jeffrey also questioned our interpretation of the pathology in phalangeal osteitis but I think sufficient has already been said to support our contention that it is actual infection of the bone and not an ischæmic necrosis. As far as active movements are concerned, we feel that these are applicable in cases of tendon sheath infection but we consider them contra-indicated in the other infections, except in the healing stage.



Dr Orr has mentioned procaine penicillin. So far, we have not employed it in the treatment of our cases but I am sure the introduction of a satisfactory preparation which will allow a single daily dose of the drug will be of great value in the treatment of these cases. We have so far had no evidence, as Mr Cameron and Mr Porter have already pointed out, that the sensitivity of the organisms, with which we are dealing, to penicillin has in any way altered, as yet.

#### ADDENDUM

Further reference to the records show that no case of finger pulp infection in either of these two groups of our cases in which early and adequate incision has been employed has shown phalangeal osteitis.

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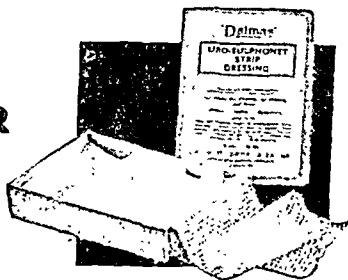
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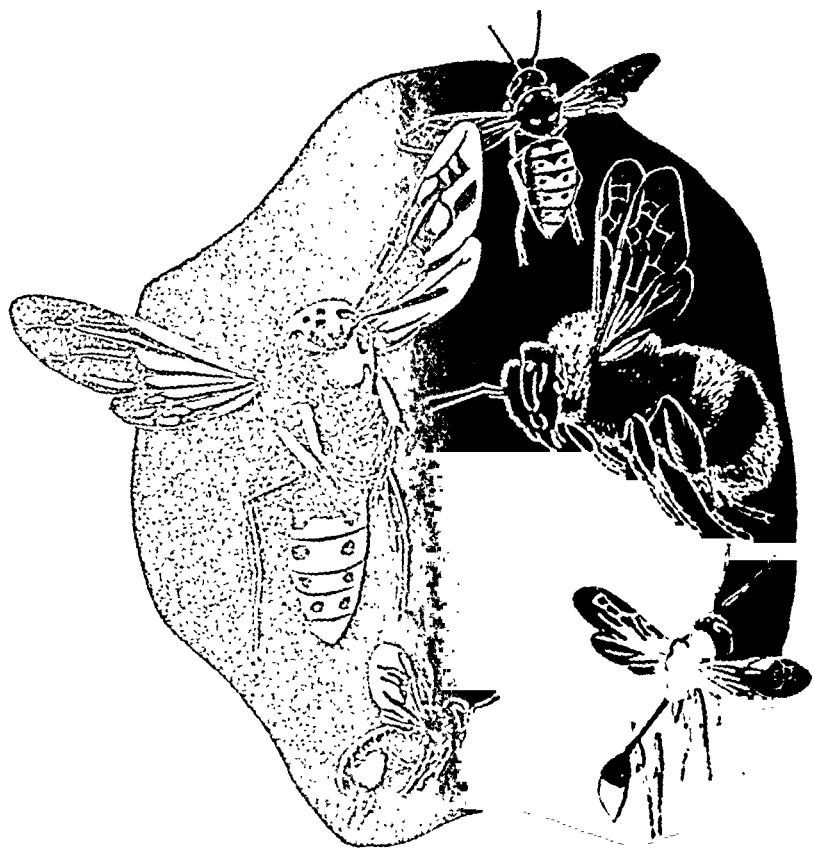
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# Edinburgh Medical Journal

June 1949

## SOME PROBLEMS IN THE DIAGNOSIS OF MENINGEAL TUBERCULOSIS

By W. M. JAMIESON, M.D., D.P.H.

Physician-Superintendent, King's Cross Hospital, Dundee

IT is, I think, becoming increasingly clear that the fatality rate in tuberculous meningitis treated with streptomycin bears no small relationship to the stage of disease at which treatment is instituted. The importance of early diagnosis has made us conscious of the many difficulties associated therewith, and in particular much attention has had to be focused on lymphocytic exudates (and sometimes polynuclear too) in the cerebro-spinal fluid. In King's Cross Hospital, Dundee, where a streptomycin treatment centre has been in operation for about eighteen months, we are fortunate in having thirty beds available for the observation and treatment of children suffering from either pulmonary or non-pulmonary tuberculosis. Most of the pulmonary cases are discovered by routine examination of contacts, and with a comparatively small waiting list the period between diagnosis and admission to hospital is not lengthy.

The children are nursed in a bright well-ventilated ward with adequate balcony facilities. They are kept in bed—I would hesitate to say at rest, for that is impossible when dealing with this type of patient who is, most often, an extremely lively and to all outward appearances a normal child. They are given a good mixed diet and their appetites are usually, to put it mildly, unimpaired. Temperature, pulse and respiration rates are recorded twice daily and serial X-rays are taken at intervals of one to two months. I draw this picture because it is of considerable importance in establishing a base-line of primary tuberculosis which may later be altered by the occurrence of meningitis. Thus it is possible to assess the "normal" in each patient admitted and at the least sign of departure from this immediate steps are taken to ascertain the reason. It is becoming very evident that thecal puncture is one of the first essentials. In little more than a year, an abnormal cerebro-spinal fluid was found in no fewer than 8 of 57 children under observation, and it is with the consideration of these that this paper is mainly concerned.

Read at a meeting of the Tuberculosis Society of Scotland held at Dundee on 1st April 1949.

## CASE RECORDS

CASE NO. 1.—(J. McL.), a female child, aged  $1\frac{3}{4}$  years, was admitted on 28th January 1948 with a family history of tuberculosis, a positive Mantoux and radiological evidence of right hilar adenitis with the later development of opacity of the entire upper lobe of the right lung. In spite of this she remained quite well until 7th March when she was sick and listless, had loose stools and a rise of temperature. She was better over the next few days, but on 11th March sickness recurred and she became irritable. Lumbar puncture gave the following results: fluid under increased pressure; cells 200/c.mm. mainly lymphocytes; protein 50 mgms. per cent.; Lange 5555444322. Fluid was injected into a guinea-pig, which, killed at 8 weeks, was found healthy, and two cultures were also negative for *B. tuberculosis*. These were, of course, retrospective findings, and treatment with streptomycin had begun on 11th March (*i.e.* 5th day of symptoms). Response to therapy was good, the temperature subsiding in a week and the clinical condition returning to normal. Treatment was stopped after 16 weeks. Serial cell counts over the next 7 months showed a gradual return to normal (200, 185, 270, 110, 37, 20, 14, 17, 64, 10, 12, 10, 3). Two post-treatment samples of C.S.F. were cultured and also inoculated into guinea-pigs with negative results. At the beginning of October 1948 (*i.e.* a full 7 months after the initial onset of meningitis) there was a relapse with clinical signs of meningitis and an abnormal C.S.F. This time three cultures of C.S.F. were all positive for *B. tuberculosis* (human type) and two inoculated guinea-pigs were both found suffering from tuberculosis. The relapse failed to respond to streptomycin and the patient died on 15th November.

Post-mortem examination showed:—

- (1) Tuberculous meningitis.
- (2) Tuberculoma in wall of lateral ventricle.
- (3) Primary lung focus.
- (4) Caseating hilar gland.

CASE NO. 2.—(R. D.), a male child, aged  $1\frac{3}{4}$  years, was admitted to hospital on 7th October 1947 with a history of tuberculous cervical glands and radiological appearances of a miliary lesion in the lungs. On admission, Mantoux test was positive, gastric lavage negative and there was radiological evidence of right hilar enlargement only. He was quite well until 21st March 1948, when he became pyrexial and over the next few days developed malaise, headache, anorexia and lethargy. Lumbar puncture on 25th March (*i.e.* 5th day) gave the following results: pressure increased, cells 320/c.mm., mainly lymphocytes; protein 90-100 mgms. per cent.; sugar present. Two cultures of C.S.F. were negative for tubercle bacilli, but an inoculated guinea-pig was found to be suffering from tuberculosis (minimal lesion). Treatment with streptomycin had been begun with apparently good effect, although after 4 months the cell count in the C.S.F. was still 128/c.mm. and a post-treatment sample inoculated into a guinea-pig gave a positive result. On 31st July (*i.e.* a little more than four months after the initial meningitis), there was a relapse. The cultures failed to produce an organism, but once again an inoculated guinea-pig developed tuberculosis. Streptomycin therapy was re-started with good effect and the child is at present well. The latest cell count is 20/c.mm. and a sample submitted for "test of cure" has been reported negative.

CASE No. 3.—(C. B.), a male child, aged  $\frac{6}{12}$  year, was admitted on 12th March 1948 with a definite family history of tuberculosis, Mantoux positive, gastric lavage positive (human type) and radiological evidence of a primary complex in the right lung. The infant remained well for less than three weeks, and on 31st March he appeared listless, had loose stools and became pyrexial. Lumbar puncture on 5th April (*i.e.* 6th day) gave the following results: C.S.F. under increased tension; cells 230/c.mm., mainly lymphocytes; protein 100 mgms. per cent.; sugar absent; Lange 3334445554. *B. tuberculosis* (human type) was cultured from the fluid and guinea-pig inoculation was positive. In spite of streptomycin therapy his condition deteriorated steadily till death on 15th June (*i.e.* ten weeks after the start of treatment). Permission for post-mortem examination was not granted.

CASE No. 4.—(R. L.), a male child, aged 3 years, was admitted to hospital on 12th March with a history of a primary lung complex  $\frac{1}{12}$  year previously, the present reason for admission being tuberculous disease of the spine (L.V. 1 and 2). Mantoux reaction was positive and gastric lavage negative. He was apyrexial and appeared well generally until 15th April when he was actively sick and next day became listless and drowsy, with twitching of the left arm. In the evening he had two convulsions, and lumbar puncture done the same evening (16th April) gave the following results: cells 50/c.mm., mainly lymphocytes; protein 20 mgms. per cent.; sugar present; Lange 10×0. Three cultures failed to reveal an organism and an inoculated guinea-pig, killed at eight weeks, was found healthy. The response to streptomycin therapy was rapid and the cell count gradually returned to normal over two months. Post-treatment samples of C.S.F. failed to show tubercle bacilli. He has now been observed for more than ten months and is clinically well from the meningitic viewpoint and cells in the C.S.F. are less than 1/c.mm.

CASE No. 5.—(M. McD.), a female child, aged 4 years, was admitted on 30th April 1948, with a family history of tuberculosis, positive Mantoux reaction and radiological evidence of a primary complex in the lower zone of the right lung. Apart from slight loss of weight she was quite well until 12th June when the temperature rose sharply and clinical appearances suggested acute appendicitis. The condition, however, subsided over the next 48 hours, but she again became pyrexial and was listless. Lumbar puncture was done on 17th June (*i.e.* 5th day) with the following results: pressure increased; cells 340/c.mm., mainly lymphocytes; sugar absent; protein less than 10 mgms. per cent.; Lange 1122220000. Three cultures of C.S.F. were negative for *B. tuberculosis*, and an inoculated guinea-pig, killed at eight weeks, was healthy. Treatment with streptomycin had been begun. After one week the child was apyrexial and apparently "normal" again. The pleocytosis gradually subsided and the C.S.F. was normal in twelve weeks. A post-treatment sample of fluid was cultured and inoculated into a guinea-pig with negative results. X-ray examination at the end of December showed the primary complex apparently healed and she was discharged from hospital on 24th January 1949. She has remained well to date (*i.e.* about nine months from the onset of meningitis).

CASE No. 6.—(S. E.), a male child, aged  $1\frac{1}{2}$  years, was admitted to hospital on 22nd July 1948 with Mantoux positive, gastric lavage negative and radiological evidence of a primary complex in the midzone of the right lung. He

remained well and apyrexial for just over three weeks but on 15th August he was very sick, listless and pyrexial. Lumbar puncture was performed next day (16th August) with the following result: pressure increased; cells 124/c.mm., mainly lymphocytes; sugar present. Two cultures failed to reveal tubercle bacilli and an inoculated guinea-pig, killed at eight weeks, was found healthy. There was a good response to streptomycin therapy, and the C.S.F. was normal cytologically after two months. Treatment was discontinued after 16 weeks and on 7th January 1949 a specimen of C.S.F. was submitted to the bacteriologist for "test of cure." In spite of the fact that the C.S.F. was chemically and cytologically normal, *B. tuberculosis* was cultured from this sample. The child has now been under observation for seven months and has remained well. A further sample of fluid has been cultured and inoculated into a guinea-pig with negative results.

CASE NO. 7.—(J. C.), a female child, aged 11 years, was admitted on 28th June 1948 with tuberculous disease of the cervical spine (Mantoux positive, gastric lavage negative, X-ray chest normal). She was apyrexial and quite well generally till the end of August when she complained of recurrent headache. She was apyrexial and there were no signs of meningeal irritation, but lumbar puncture on 2nd September gave the following results: pressure normal; cells 145/c.mm., mainly lymphocytes; sugar normal; protein 50 mgms. per cent.; Lange 10×0. Two cultures of C.S.F. were later reported negative for *B. tuberculosis* and an inoculated guinea-pig killed at eight weeks was healthy. Meanwhile streptomycin therapy had been begun on 2nd September. The clinical condition quickly returned to normal (it was never far removed), and when treatment was discontinued after sixteen weeks she was apparently well. She had been off treatment for only ten days when she began to have infrequent bouts of sickness and headache. On 10th January 1949 treatment was restarted but she continued to have bouts of headache and sickness, being apparently normal in the intervals. On 10th February she had double vision and there was paralysis of both 6th nerves. She died quite suddenly on 12th February. Cultures and guinea-pig inoculation of the C.S.F. were negative, but post-mortem examination confirmed the diagnosis. A summary of the findings was as follows:—

- (1) Caseous mesenteric gland.
- (2) Healed scar upper right lung.
- (3) Caries 2nd and 3rd cervical vertebrae.
- (4) Gross dilation of lateral ventricles with tuberculoma in wall of the right ventricle. Thin basal film of exudate (both 6th nerve nuclei involved).

Summarising the findings, therefore, lymphocytic exudates, with relatively minimal clinical signs, developed in seven children under observation for known tuberculous lesions. The essential features are summarised in Table I. It will be seen that the most constant clinical features were listlessness, pyrexia and sickness in that order. In only two cases (Nos. 2 and 3) was the diagnosis of tuberculous meningitis confirmed at the onset by recovery of the organism. A further three were confirmed at later dates (Table II) and the position to date is that only two remain unconfirmed bacteriologically.

The lack of bacteriological confirmation led us to consider the nature of the occurrence of many of these lymphocytic exudates. In order to establish a base-line it was decided to perform thecal puncture

TABLE I

*Clinical Details in 7 Patients with a Known Tuberculous Lesion who Developed Lymphocytic Exudate in C.S.F.*

Case.	Site of Initial Lesion.	Symptoms—Meningeal Involvement.		C.S.F.							
		Symptoms.	Duration (Days) before L.P.	at Initial Thecal Puncture.						Culture.	G. Pig.
				Appear.	Pressure.	Cells/cmm.	Sugar.	Protein.	Lange.		
1. (J. McL.)	Lung	Listlessness, pyrexia, sickness, diarrhoea	4	Cl.	+	200	+	50	Early	—	—
2. (R. D.)	Lung	Lethargy, pyrexia, headache, anorexia	5	Cl.	+	320	+	90	...	—	+
3. (C. B.)	Lung	Listlessness, pyrexia, diarrhoea	5	Cl.	+	230	—	100	Late	+	+
4. (R. L.)	Lung Spine	Listlessness, sickness, twitching, anorexia	2	Cl.	N.	50	+	20	N.	—	—
5. (M. McD.)	Lung	Lethargy, pyrexia, abdominal pain	5	Cl.	+	340	—	10	Mid.	—	—
6. (S. E.)	Lung	Listlessness, pyrexia, sickness	2	Cl.	+	124	+	...	...	—	—
7. (J. C.)	Spine	Headache	3	Cl.	N.	145	+	50	N.	—	—

in a group of children with a primary lung complex but who were otherwise normal (*i.e.* apyrexial and well generally). This was done in sixteen children, in each of whom the C.S.F. was found to be normal,

TABLE II

*Showing Results of Attempts to Confirm Infection of Meninges with B. Tuberculosis*

Case.	Organism Isolated.				Organism not Isolated.
	Onset.	"Test of Cure."	Relapse.	Post-mortem.	
2. (R. D.) . . .	+	...	+	...	...
3. (C. B.) . . .	+	...	...	...	...
6. (S. E.) . . .	...	+	...	...	...
1. (J. McL.) . . .	...	...	+	...	...
7. (J. C.) . . .	...	...	...	+	...
4. (R. L.) . . .	...	...	...	...	+
5. (M. McD.) . . .	...	...	...	...	+

chemically and cytologically. In a further group of six children, all with a primary tuberculous lesion but who had been "out of sorts," the C.S.F. again showed no apparent abnormality. Bacteriological examination was not carried out in either group.



CASE No. 8.—(W. C.), a male child, aged  $4\frac{1}{2}$  years, was admitted to the tuberculosis unit on 18th June 1948, having been transferred there from another ward in the hospital following an attack of whooping cough complicated with pneumonia. The Mantoux test was positive and there was radiological evidence of a primary tuberculous lesion in the lower zone of the left lung. There was no family history of tuberculosis. On 24th August 1948, lumbar puncture was done for experimental purposes referred to above, and the fluid was normal. On 27th August he was very sick and there were definite clinical signs of meningeal irritation. Lumbar puncture (27th August) gave the following results: pressure normal; cells 150/c.mm. (lymphocytes); protein 50 mgms. per cent.; sugar present; Lange reaction  $10\times 0$ .

As he was not particularly drowsy, and bearing in mind previous experience, streptomycin therapy was withheld temporarily. Within 48 hours signs and symptoms had disappeared and the cerebro-spinal fluid returned to normal in 14 days. A culture of the initial abnormal C.S.F. was unfortunately contaminated, but an inoculated guinea-pig, killed at eight weeks, was found healthy. The child remains well to date, approximately seven months after the occurrence of meningeal involvement.

### DISCUSSION

Several general conclusions may be made from the study of this small investigation. Firstly, primary tuberculosis, *per se*, does not appear to cause any abnormality, chemical or cytological, in the cerebro-spinal fluid. I have no evidence as to whether organisms may or may not be present. Secondly, minor upsets in children suffering from primary tuberculosis may or may not be associated with an abnormal C.S.F. Lastly if a lymphocytic exudate *is* present it may or may not be possible to demonstrate tubercle bacilli in the fluid.

It is in the proper interpretation of a lymphocytic exudate occurring in a child known to be suffering from tuberculosis that difficulty has been encountered. The causes of lymphocytic exudate in C.S.F. are many and cover the fields of primary viral infections, secondary post-infective meningo-encephalitis and a miscellaneous group of infections due to bacteria, spirochætes, yeasts, etc. While investigation for virus agents was not done, it seems reasonable to assume that in a child hospitalised with a primary tuberculous lesion the occurrence of a lymphocytic exudate in the C.S.F. is most likely to be associated with the tuberculous infection, either because of a true tuberculous meningitis or a serous meningitis of tuberculous ætiology.

Rich and McCordock in 1933 questioned the original view that tuberculous meningitis was due to a direct hæmatogenous infection of the meninges. They found focal caseous lesions, in communication with the meninges, older than the meningitis in 77 out of 82 brains studied. McGregor and Green confirmed these findings in 74 out of 88 cases examined. While several writers have not agreed with this concept, there is, I think, a growing belief that it is the correct one and that tuberculous meningitis is secondary to a focus in the choroid plexus or a focus in the brain itself, communicating with the ventricular

system or the subarachnoid space. If this view is accepted then it makes it easier to understand the possible pathogenesis of serous meningitis of a tuberculous nature, which may well be due, as suggested by Lincoln, to a perifocal reaction around a tuberculous focus already established in the brain. Furthermore, such a pathology would appear to fit the variations in the clinical picture of serous meningitis which have been reported.

MacGregor and others (1934) described three patients with primary tuberculosis who developed meningeal signs and in whom tubercle bacilli were recovered from the C.S.F., the fluid being abnormal cytologically and chemically in only one. Choremis and Vrachnos (1948) described two patients in whom tubercle bacilli were isolated by culture from the C.S.F., the fluid being virtually normal chemically and cytologically (one patient had 8 cells/c.mm. and chloride was said to be 540 mgms. per cent.). This picture of organisms without cellular reaction contrasts with the opposite picture of cells without organisms described by Lincoln (1947). She described twelve cases of serous tuberculous meningitis. In eight of these the diagnosis was apparently made on clinical evidence of meningeal irritation alone, there being no changes cytologically, chemically or bacteriologically. In the remaining four, lymphocytic pleocytosis was present without chemical or bacteriological changes. Rubie and Mohun (1949) have recently reported five patients showing evidence of tuberculous infection who developed "meningism" with an abnormal C.S.F., who were not treated with streptomycin and who all recovered, the C.S.F. reverting to normal in periods varying between 2 and 23 days. There is no indication in the paper as to whether *B. tuberculosis* was or was not present in the fluid.

The findings in my own series of cases are complicated by the fact that all but one were treated with streptomycin on the evidence of a lymphocytic exudate in the C.S.F. in the presence of a known primary tuberculous lesion. It seems more than possible that several of these patients might well have recovered, initially at least, *without* streptomycin. One case (No. 3) was obviously suffering from tuberculous meningitis from the start. In the two patients (Nos. 1 and 7) who died following a relapse, post-mortem examination showed in each a tuberculoma in the wall of the lateral ventricle, and their initial symptoms could presumably have been due to a perifocal reaction. MacGregor and others (1934) refer to the work of Cramer and Bickel who collected 46 cases of recovery from tuberculous meningitis, confirmed by demonstration of the organism, and who stated that "in many of these recovery was temporary and death followed within a few months from recurrence of meningitis or from the effects of tuberculosis elsewhere." The remaining five patients in my series (four treated, one untreated) are all well to date. Of these, two are confirmed and three unconfirmed bacteriologically. The untreated case was presumably suffering from serous meningitis, and I believe

that at least three of the treated cases (Nos. 4, 5 and 6) may have been due to the same condition.

Lincoln attempted to differentiate between serous meningitis and tuberculous meningitis. Nothing she has written has altered my opinion that the two simply cannot be differentiated in their early stages, and that it is only the progressive nature of tuberculous meningitis that can ultimately decide.

What then is the policy to be when dealing with an abnormal C.S.F. in a child with a known tuberculous lesion? We know that the progress of tuberculous meningitis in the young child can be extremely rapid. I have recently seen a child who was irritable one day, developed a focal nerve palsy the next, was comatose the next and who failed utterly to respond to streptomycin therapy, started at the stage of the nerve palsy. Nevertheless I believe that in the majority of cases one can, at least for a day or two, watch developments in doubtful cases. Meningism, local muscular twitchings and even convulsions can occur in both conditions, while in the early stages the findings in the C.S.F. may run parallel. The factors which I believe to be of importance in indicating tuberculous meningitis are, in order of importance, increasing drowsiness and reduction of the sugar content of the C.S.F. If one or both of these factors are present, then streptomycin therapy should be begun without delay and confirmation, or otherwise, of the diagnosis awaited from the result of cultures and guinea-pig inoculation of the cerebro-spinal fluid.

### CONCLUSIONS

Since the introduction of streptomycin has altered the prognosis in tuberculous meningitis, it is now of the utmost importance that abnormality of the cerebro-spinal fluid should be recognised as early as possible in children with a primary tuberculous lesion, even although such abnormality can be explained on the basis of a benign serous reaction. It would seem that such a benign reaction may disappear without treatment and the cerebro-spinal fluid remain normal, in which case one may be justified in the presumption that the causal intracerebral lesion has healed, but obviously longer periods of observation of individual cases will be necessary before one can be certain. On the other hand, if a child has had a benign serous reaction he would require careful watching since, presumably, a true tuberculous meningitis could supervene at any time as a result of progression of the intracerebral focus. Since abnormality of the cerebro-spinal fluid can be present with minimal clinical signs, it is suggested that thecal puncture, while never to be undertaken lightly, should nevertheless be seriously considered as an early step in all cases in which there is the slightest deviation from the clinical "normal" in a child with a primary tuberculous lesion.

## ADDENDUM

Recently a further case has arisen in a male child aged 4 years. This child was in hospital with a tuberculous lesion of the upper left lung (Mantoux reaction positive, gastric lavage negative) and had been under observation for about eleven months, his general condition being good and his temperature normal. On 2nd April 1949 the temperature was elevated and next day he was complaining of headache, and was flushed, irritable and drowsy. Lumbar puncture gave the following results: fluid under markedly increased pressure; cells 6/c.mm.; sugar normal; protein 40 mgms. per cent.; Lange 2333444555. On 4th April the cells were 10/c.mm., and on 5th April were 20/c.mm. By 9th April the clinical condition had returned to normal and the C.S.F. was normal by 15th April, without streptomycin therapy. Results of cultures and guinea-pig inoculation of C.S.F. are awaited with interest.

I am indebted to Professors Tulloch and Lendrum, under whose supervision the bacteriological and pathological work respectively was carried out.

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# INDUSTRIAL SIDEROSIS

By A. T. DOIG, M.D., D.P.H.

H.M. Medical Inspector of Factories

IN text-books of medicine siderosis is usually defined as fibrosis of the lungs due to the inhalation of iron or steel dust. Actually the condition described is really silicosis, and this is not surprising, for many metal workers are exposed to silica dust. Siderosis used in this way merely denotes silicosis in a metal worker just as chalicosis denotes silicosis in a stone worker, schistosis in a slate worker, and so on. When iron and silica dusts are inhaled together it might be quite proper to describe any ensuing fibrotic condition of the lungs as a sidero-silicosis, but the present view is that the inhalation of iron dust alone, without added silica, does not cause fibrosis.

The inhalation of mineral dusts met with in industry result in varied and complex reactions. Some of them are locally caustic producing irritation of the upper respiratory tract, even to ulceration and perforation of the nasal septum; others irritate the bronchi or the lung parenchyma producing atypical forms of pneumonia, and some have long-term effects resulting in chronic changes in the lungs—diffuse in the case of asbestos, focal in the case of silica. Some have a carcinogenic action, some produce granulomata, and others appear to be able to lie quite inertly for long periods in the lung tissues without producing any permanent reaction by the tissues.

## SILICOSIS

A description of silicosis is superfluous here. The disease has received so much attention and has been discussed so often that its general features are well known. Silica dust inhalation, if the quantity of dust is large enough and the size of the particles is small enough, results in lung fibrosis of a special nature. Nodules formed of dense fibrous tissue with a concentric arrangement of the fibres are characteristic, but the deposition of fibrous tissue may be altered profoundly by accompanying infectious processes or by other dusts which modify its action. The characteristic lesion of silicosis is the deposition of fibrous tissue in an amount which is redundant and far in excess of what is required merely to shut in the dust particles.

## PNEUMOCONIOSIS OF COAL MINERS AND COAL TRIMMERS

For recent work on the etiology, pathology and the sociological effects of chronic pulmonary disease in coal miners we have to study the numerous reports from South Wales, although it is interesting to note that the earliest records came from Scotland (Gregory, 1831, Marshall 1834, Thomson 1836). Towards the end of last century and in the beginning of this century no attention seems to have been

A paper given to the Tuberculosis Society of Scotland at Dundee on 1st April 1949.

paid to the condition, and such authorities as Sir Thomas Oliver (1908) and E. L. Collis (1915) stated that the disease no longer existed. It was a period of obscurity and complacency—at least for everyone but the affected miners themselves. No compensation was payable to coal miners with respiratory trouble until 1929 and then only to workers who could prove that they had worked on silica rock. In 1934 the scheme was extended to cover miners working on the coal face and other underground workers, but still there continued much dissatisfaction. Increasing claims from the men and uncertainty as to the nature of the disease led to the Medical Research Council making an investigation which commenced in 1937. Reports were published in 1942, 1943, and 1945. These showed a serious incidence of radiological abnormalities, associated with symptoms and impairment of function, in coal-face workers and also, and this is important, in coal trimmers. This was interesting from the etiological point of view, for whereas it could be argued that the coal getter, working at the coal face, might inhale not only coal dust, but also dust from silica rock generated by other workmen, this could not be so in the case of the coal trimmers, who were exposed to dense clouds of coal dust in the holds of ships, but not to rock dust. The Medical Research Council investigators described an appearance in abnormal radiographs of a fine network—sometimes sharp and lacelike in appearance, more often blurred—which they called reticulation, and which was clearly occupational in origin. This condition was subsequently made compensatable by the Workmen's Compensation Act, 1943, which defined pneumoconiosis as "fibrosis of the lungs due to silica dust, asbestos dust or other dust, and including the condition of the lungs known as dust reticulation."

Our knowledge of the effects of coal dust in the lungs is due mainly to the work of Gough and his co-workers in Cardiff (Gough, 1947; Heppleston, 1947; etc.). They have shown that the essential lesion in the pneumoconiosis of coal workers is quite different from that of silicosis. In early pneumoconiosis of miners examination shows deposition of dust in the lymphoid tissue around the bifurcation of the respiratory bronchioles, but even in cases where there are X-ray changes there may be at first no tissue reaction. Later, a little fibrous tissue is laid down and the nodule retracts slightly assuming a stellate appearance. The fibrous tissue is, however, slight in degree and is not whorled. It may be said that this is merely a difference in degree depending upon the amount of silica in the dust inhaled. However, accompanying this slight retraction there occurs a well-marked emphysema in the air cells immediately adjacent to the nodule, thus forming a focal emphysema throughout the lung. This is a fundamental difference, for emphysema, for some reason that we do not know, is a relatively minor change in relation to the silicotic nodule while it is the most striking lesion in relation to the coal nodule. Curiously, also, it does not seem proportionate to the degree of fibrosis.

## INERT DUSTS

Certain dusts, among them iron and tin, appear to be quite inert when inhaled into the lungs. The particles are deposited in the lymphoid aggregations just as coal dust is. There they lie inertly without leading to any reaction or change in the tissues. They produce an abnormal X-ray picture because the aggregations become relatively radio-opaque by reason of their metallic content.

Electric and oxy-acetylene welders, working on iron and steel, are constantly exposed to fumes from the work. The heat of the welding arc boils the metal which vapourises and oxidises, and the fume therefore consists mainly of iron oxide particles in a very fine state of division. X-ray films of welders who have spent many years at this work may show dust reticulation, especially if they have performed a lot of work in enclosed spaces such as boilers or tanks.

The evidence that the dust which gives rise to such well-marked X-ray changes is inert may be considered under five headings:—

1. *Clinical*.—I have been interested in welders for 16 years and have examined many hundreds. In no case have I found incapacity or diminished capacity for work that could not be explained by other reasons. I have kept in touch with some welders showing dust reticulation for most of this period and find that they continue to be well and keep at work. They not infrequently admit to having cough, and often some sputum, but in my opinion these are partly due to other factors and not merely due to the deposition of iron-oxide particles in the lungs. They have no dyspnoea and exhibit no clinical evidence of fibrosis. They have a good chest expansion and exhibit a good tolerance for exercise. These opinions are amply confirmed by numerous investigators, not only as regard welders but for other workers who are exposed to iron dust (Britton and Walsh, 1940; Groh, 1944; Sander, 1944; Lanza, 1945; McLaughlin *et al.*, 1945; Barrie and Harding, 1947, etc.).

2. *Pathological*.—Only one report has been published in the world's literature of the post-mortem findings of a welder who showed the typical X-ray changes during life. This (Enzer and Sander, 1938) was illustrated by excellent microphotographs, which showed no fibrosis round the collection of iron dust. The man died of pneumonia complicating fracture of the spine, the result of an accident. The fact that no other reports have appeared in the literature speaks for itself and suggests that the condition does not shorten life. I have been able to obtain post-mortem material from two welders who, however, did not show the typical X-ray changes during life. Although the lungs showed small aggregations of iron particles, these were not associated with fibrosis.

Further pathological evidence of the inertness of iron dust has been produced by Harding and his colleagues who in successive papers describe the post-mortem appearances in detail of five silver finishers. These men had exposure to fine iron-oxide dust for 26 to 50 years and showed typical X-ray changes due to dust. In the first four cases careful microscopical examination showed that fibrosis was completely absent. In the last case (Harding, 1948) there was a minimal amount of fibrosis of the "reticulation" type—not at all like that produced by silica. Harding thinks that in this case individual susceptibility may have been of importance, but there is always the possibility

that the iron dust at some period of this man's long working life—over 40 years—may not have been pure and may have contained silica or other fibrosis-producing constituent.

3. *Experimental*.—Various experiments had been made subjecting the animals to the inhalation of iron-oxide dusts. Harding, Grout and Lloyd Davies produced X-ray changes in such experimental animals but examination of the tissues showed no fibrotic or other reaction. Cappell too found that "no ill effects follow massive accumulation of iron in the liver cells." Other workers have found that iron oxides injected subcutaneously (Von Haam and Groom) or intraperitoneally behaved inertly. The late Professor Kettle's experiments might also be mentioned in this connection. He found that not only did iron alone produce no tissue reaction but that iron when mixed with silica prevented silicosis.

4. *Statistical*.—The Registrar-General in his Occupational Mortality Supplement shows that in 1931 in the group of welders and burners, numbering 11,542 in England and Wales, there were only 123 deaths compared with 161 expected on the basis of age-rates of all males. Unfortunately no more recent figures are available. I have, however, collected from various factories information regarding the sickness absence of welders in relation to other workers and find that welders are favourably placed compared with other groups, not only for total sickness, but also for respiratory illnesses. I have been asked to consider these figures as confidential and therefore unfortunately they cannot be reproduced here.

Collen and his colleagues (1944) give reliable evidence about pneumonia in welders in an analysis of the sickness rates of the 90,000 workers in the Kaiser Richmond shipyards in America. They found that there was no increased incidence in welders. Collen, in a later article (1947) confirms his earlier findings saying that the annual incidence, death rates and case fatality rates for welders were similar to all other shipyard workers, and that the cases were similar in severity, required the same number of days for treatment and showed no difference in the incidence of complications.

5. *Radiological*.—The presence of pulmonary fibrosis in and around dust aggregations cannot be diagnosed from an examination of single X-ray films; the film of a welder may be indistinguishable from that of a sandblaster with silicosis, or a miner with pneumoconiosis. The small densities forming reticulation or nodulation may be due to a variety of conditions of which nodular fibrosis is only one. However, the X-ray changes in silicosis, asbestosis, and pneumoconiosis are permanent; if they change at all it is in the direction of progression, and this is common. McLaughlin and I, however, recently described two of our original welders whose X-ray appearances have changed for the better (Doig and McLaughlin, 1948). We showed that one man, who exhibited definite X-ray changes of the dust inhalation type in 1934, and who ceased welding on being told of these changes, now has an X-ray picture within normal limits. The pneumoconiosis has resolved, and no one could guess at its previous existence. The other man who had marked changes in 1933, and who continued to work as a welder, became a welding instructor in 1940, with consequent great diminution in his exposure to fume; his X-ray film now shows partial clearing of the abnormal shadows.

Other dusts which are considered on present evidence to be inert include tin, calcium, and barium, but much more knowledge is



required before we can be sure that this is so. Tin is much more radio-opaque than iron, therefore deposits of tin in the lungs cause particularly dense shadows. Pendergrass and Pryde (1948) show an X-ray film of this type, discovered on routine examination, the subject being a man aged 45 years who had bagged tin oxide for fifteen years. There was no disability.

I have said no word about hæmatite miners, although there are a number of reports in the literature about the effects on the lungs of iron-ore dust. There is no doubt that hæmatite miners may get a disabling pneumoconiosis, but this is to be expected for iron ore is a rock with considerable silica content, and so the disease is really a silicosis or at least sidero-silicosis. Some hæmatite miners working in mines with soft ore may develop X-ray changes without incapacity, and in such cases it may be assumed that the siderosis element predominates over the silicosis.

Although I have referred only very briefly to the evidence, I think I have said enough to show that industrial siderosis is one of the benign pneumoconioses and that iron is one of the inert dusts. One of the practical lessons to be learned is that by looking at an X-ray film one cannot diagnose silicosis; one requires in addition to the X-ray evidence a complete industrial and clinical history and the results of a clinical examination. The radiologist must primarily describe what he sees in the film. He does not see pathological changes. He must not assume the presence of fibrosis when X-ray examination shows reticulation or nodulation. If he does so there are liable to be unfortunate repercussions on the patient, on his family, and on industry.

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## PULMONARY HÆMOSIDEROSIS

By ALAN C. LENDRUM, M.A., M.D., B.Sc.

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IT has been known for long to radiologists that mottled shadows are sometimes seen in the skiagraph of the lungs of patients with mitral stenosis. These shadows were frequently described as miliary congestion, but more recent study has shown the permanent character of the picture, and it is now certain that the anatomical explanation is a deposition in the lung of hæmosiderin (Scott *et al.*, 1947). These focal deposits have been found in all of a series of cases of long-standing mitral stenosis, with the exception of those where there was an accompanying stenosis of the tricuspid valve. In this latter exceptional group there is usually no hypertrophy of the myocardium of the right ventricle.

The actual nodules consist of a group of adjacent alveoli packed full with phagocytes loaded with hæmosiderin—siderophores—the so-called heart failure cells; these filled alveoli frequently show some thickening of their walls, contrasting markedly thereby with the normal thin-walled alveoli of the lung between the foci. In the tissues near the affected alveoli there is ferrous impregnation of the elastic tissue of the vessels, followed by rupture of the elastica and the development of giant cell reactions and a diffuse fibroblastic activity. Obvious crystals are formed in this stromal tissue and these, like the fragmented elastica, also elicit a foreign-body reaction. The depositions of iron suggest that iron escapes in soluble form from the depots of hæmosiderin; they recall the incrustations in the spleen in certain anæmias.

The sharply circumscribed nature of the foci and their situation in the alveolar part of the lung point to the mode of development. It seems reasonable to assume that the congregation of siderophores must be in the very alveoli into which a previous hæmorrhage had occurred, and that the hæmorrhages could be distributed in these groups of alveoli, only if the blood reached the alveoli from the terminal air passage belonging to that particular group of alveoli. It is in the wall of these respiratory bronchioles that there is situated the capillary anastomoses between the pulmonary and bronchial arteries, and Ferguson *et al.* (1944) describing this site in cases of mitral stenosis liken the condition of the mucosal vessels to the varicosity at the foot of the œsophagus in portal cirrhosis.

Acceptance of this mechanical explanation of the hæmorrhages does not mean that we must postulate cardiac failure before hæmorrhage can occur. But it does imply that similarly situated hæmorrhages

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could occur if the balance between the ventricles were upset by a low intensity failure of the left ventricle. That this does in fact happen has now been shown by the finding in the lung, from cases of hypertension who have survived periods of left ventricular failure, of hæmosiderin deposits of exactly the same type as are found in the cases with mitral stenosis.

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*p*-AMINOSALICYLIC ACID (P.A.S.)

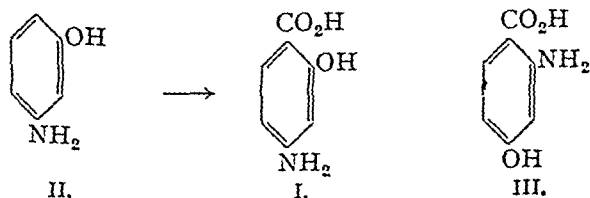
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## INTRODUCTION

It was observed by Bernheim (1940, 1941) that the presence of derivatives of benzoic acid and salicylic acid effect a considerable increase in the oxygen uptake by tubercle bacilli. Lehmann (1946) examined a series of derivatives of these two acids with the object of testing their inhibitory effect upon the growth of tubercle. In the course of this work it was observed that *p*-aminosalicylic acid (P.A.S.) (I) effected a 50-75 per cent. inhibition of growth at a dilution of 1:650,000. Limited clinical experience in Sweden, America, Switzerland and in this country have established a *prima facie* case for a detailed clinical evaluation of P.A.S. and its derivatives in the treatment of human tuberculosis (for bibliography see Drain, Martin, Mitchell, Seymour and Spring, (1949)).

## METHODS OF PREPARATION

Detailed clinical evaluation was hampered by the relative inaccessibility of P.A.S. The preparative routes available, involved a synthesis of 4-nitrosalicylic acid which was reduced to the required P.A.S. In view of the relatively large quantity of P.A.S. required for an adequate clinical evaluation (15-25 gm. per day to maintain a blood level of approximately 7-10 mgm. per 100 c.c.) efforts were made to devise an alternative method for its preparation. In association with Mr D. E. Seymour of Herts Pharmaceuticals, Ltd., Welwyn Garden City, various new routes and modifications of alternative routes were examined. Of these one proved to be considerably simpler than the others. In this, *m*-aminophenol (II) which is a relatively readily available coal-tar product, is heated with potassium or sodium bicarbonate using a variety of reaction conditions to yield a product from which P.A.S. in a high state of purity is readily isolated (1948):—



Read at a Symposium on the Use of P.A.S. in the Treatment of Tuberculosis  
at the Robroyston Hospital, Glasgow, on 28th January 1949.

After this method had been developed, we found that the reaction had previously been described in the patent literature (D.R.P. 50835), the reaction product being described simply as a *m*-aminophenol carboxylic acid. It was conceivable that the reaction product consisted of 4-hydroxyanthranilic acid (III) or contained a proportion of this isomer. We showed that the reaction product consists of pure P.A.S., the identity being established by comparison with a specimen of acid obtained by the reduction of *p*-nitrosalicylic acid, by comparison of corresponding derivatives of the two preparations and by the comparison of the ultraviolet and infra-red absorption spectra of the two acids. In addition, *p*-hydroxyanthranilic acid (III) was prepared by an unambiguous route; its ultraviolet absorption spectrum is markedly different from that of P.A.S., a property which allows it to be readily distinguished from P.A.S.

### STABILITY

Concerning the stability of P.A.S., detailed studies by Oberweger, Seymour and Simmonite (1948) have shown that in strong acid solution it is relatively unstable, undergoing decarboxylation to produce the toxic *m*-aminophenol. The crystalline sodium salt is, however, stable and its ready solubility in water gives it great advantages over the free-acid.

A series of functional derivatives of P.A.S. have been prepared and *in vitro* tests of their inhibitory effect upon pathogenic strains of tubercle bacilli have been made by Goodacre, Mitchell and Seymour (1948). Of these derivatives, the isobutyl ester of P.A.S. appears to be the most promising.

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# PARA-AMINOSALICYLIC ACID IN PULMONARY TUBERCULOSIS

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OUR experience of the use of para-aminosalicylic acid (P.A.S.) in the treatment of tuberculosis is limited to the observation of 13 patients in whom the drug was administered by the oral route. Eleven cases were of chronic lung tuberculosis, all with cavitation; one case was of pleural effusion associated with a marked degree of toxæmia; and one case was of chronic disseminating tuberculosis.

In view of the wide variation in dosage which has been employed and the importance stressed by Erdei and Snell (1948) of regarding each brand of P.A.S. as a different substance, it is felt that an outline of the dosage and preparation used will help in the appreciation of the results which have been obtained. Throughout, the sodium salt of para-aminosalicylic acid as supplied by Herts Pharmaceuticals Ltd. has been used. It has been given orally in 10 per cent. solution and was flavoured with liquorice. We have employed a daily dosage of 15 gm. divided into five 3-gm. doses given at three-hourly intervals from 9 a.m. to 9 p.m. The drug has been given for twelve to fourteen weeks in all but one patient who has been treated continuously for twenty-four weeks. The daily dosage is thus similar to that employed by Lehmann (1946*a*), Vallentin (1947) and Erdei and Snell (1948) but considerably less than has been recently recommended.

## BLOOD LEVELS

It is important in assessing clinical results, toxicity of the drug, and the effect upon the tubercle bacillus to know the blood levels of the drug which have been obtained. Vallentin (1947) has stated that blood levels vary widely in different individuals and Alin and Difs (1947) report that not only does the absorption vary from patient to patient but also from time to time in the same individual. With a dosage similar to ours these authors reported blood concentrations varying from 2 to 10 mgm. per cent. Our experience is very similar and blood levels varying from 2 to 7 mgm. per cent. have been observed. No direct correlation between blood levels and clinical effects has been observed.

## TOXICITY

The chief toxic symptoms which have so far been described have been of gastro-intestinal disturbance—nausea, vomiting and diarrhœa. Only one case in our series has shown any such toxic effect. One

A paper delivered to the Tuberculosis Society of Scotland on 28th January 1949 as part of a Symposium on Para-aminosalicylic Acid.

patient vomited after the administration of each dose. The drug was withdrawn and no further vomiting occurred. None of the other 12 cases was in the least disturbed by the taking of the drug. The freedom from gastro-intestinal symptoms in these cases is probably due to the use of the sodium salt and the relatively low dosage employed.

One case developed what appeared to be true drug sensitivity twelve days after commencing treatment. This was manifested by the onset of a rigor within two minutes of taking the drug followed by a rise of temperature of  $105^{\circ}$  F. This was accompanied by paroxysms of coughing, pain in the teeth and jaws and suffusion of the face and conjunctivæ. An erythematous rash also occurred on the trunk and limbs. An attempt was made to administer the drug under the cover of anti-histamine drugs but this proved unsuccessful. This case has now been successfully desensitised by the initial use of very small doses, commencing with a dose of 0.1 gm. five times a day at three-hourly intervals and increasing the unit dose every five days by 0.1 gm. Fifteen gm. daily is now being given without any toxic effect.

### CLINICAL RESULTS

In presenting the clinical results obtained reference will be made only to the 9 cases who have completed treatment.

One very spectacular result has been achieved. A man of 45 who gave a history of right-sided pleurisy with effusion subsequently developed a nodular infiltration of the right upper lobe with a positive sputum, and tuberculous abscesses related to sternum and the tenth rib. His general condition was poor and he had been continuously febrile—up to  $100^{\circ}$  F. and over—for a period of twelve months prior to the commencement of treatment with P.A.S. After two days' treatment the temperature became normal and remained so, there was a great improvement in his general condition and his weight steadily increased by 14 lb. His B.S.R. fell from 98 mm./hr. (Westergren) to 6 mm./hr. The rib abscess failed to fill up again after aspiration and the sinuses related to the sternal abscess showed definite signs of healing. The sputum was reduced from 4 to 1 drachm daily, became thin and mucoid in character, and tubercle bacilli have never been isolated from it since. These changes took place gradually over a period of three months.

In the other 8 cases, the clinical results obtained have been much less spectacular. In two cases, the effects observed during treatment have been contributed to by the simultaneous use of collapse therapy, and in two others by the tendency towards improvement which is inherent in the natural history of their disease. In all but one there was a slight but definite general clinical improvement manifested by an increased sense of well-being, improved appetite and a gain in weight varying from 4 to 10 lb. One patient lost at least 7 lb. during treatment. In 3 cases where fever was present this subsided without sweating.

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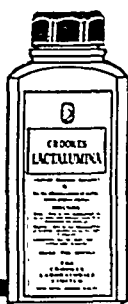
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In 5 cases cough became less and the sputum became thinner and less purulent. The B.S.R. showed a significant fall in all cases, the maximum effect usually occurring within a month. In those cases in whom the B.S.R. did not fall to within normal limits, there was a tendency for the B.S.R. to rise again after the tenth week. Slight improvement in the radiological appearances of the disease has been noted in 4 cases, no change was observed in one, and two showed definite deterioration. A striking reduction in the size of a large dorsal lobe cavity was seen in one case and the cavity wall became appreciably thinner. This change was observed after six weeks but the cavity had returned to its original state after eleven weeks. No significant change in tuberculin sensitivity was observed except in one case who showed a temporary slight reduction in sensitivity. In most cases, the maximum clinical improvement was observed after about four weeks ; in one case improvement began only after ten weeks' treatment. One case showed definite clinical and radiological deterioration after ten weeks whilst still receiving the drug.

One of our cases was complicated by diabetes mellitus. Vallentin (1947) reports one case complicated by severe diabetes mellitus who died during treatment with P.A.S. In our case there was a striking amelioration of the diabetes following the administration of P.A.S., the daily insulin requirement falling from 132 to 92 units. Following the cessation of treatment there was a sharp rise in the insulin requirement to 112 units at which level it has become stabilised. An amelioration of the diabetic state is accepted as an indication of improvement of the tuberculous disease and the striking improvement which took place during treatment with P.A.S. is of considerable interest.

### EFFECTS ON THE TUBERCLE BACILLUS

The original observation made by Lehmann (1946b) of the inhibitory effect of P.A.S. upon the tubercle bacillus makes the study of the effect upon the organism in the cases under treatment of especial interest. Reference will be made only to the 9 cases who have completed treatment as insufficient data has been collected so far in respect of the others.

Of these nine, three have become sputum-negative on direct smear examination and culture. Of these three, one had a pneumothorax induced three days after the commencement of P.A.S. therapy and one had previously shown sputum conversion on bed rest alone and had re-converted. The third one was the patient with chronic disseminated tuberculosis to whom reference has already been made. Two became negative for a four-week period, the sputum again becoming positive at the tenth week. Four have remained positive throughout, even on direct examination. In three cases only out of the nine observed have the morphological changes in the appearance of the organism described in previous reports been seen.

One further observation has been made which may be of considerable importance. Examination of the direct smears obtained from the 4 cases who have remained positive throughout showed a marked and progressive diminution in the number of tubercle bacilli per high power field in 3 cases up to the eighth week (the decrease in one case being fifty-fold). In the fourth case the number was practically unchanged. At the tenth week, however, the number of tubercle bacilli became markedly increased and has remained so in all 4 cases. It is emphasised that these changes occurred while the drug was still being administered. Furthermore, at Professor Cameron's suggestion, cultures from sputum were set up on Loewenstein Jensen medium from each patient undergoing treatment, first at weekly and then at fortnightly intervals. A recording was made of the number of days after the sowing of the culture at which growth was first evident on naked-eye examination of the culture. In the cultures obtained from the 4 patients whose sputum has remained positive throughout a significant observation has been made. In each of these patients there was a steady slowing of the rate of development of the growth up to the eighth to tenth week. In the first case, the initial recording was fourteen days, at the tenth week sixty-one days; in the second case, sixteen days and at the ninth week forty-five days; in the third case, eighteen days and at the tenth week fifty days; in the fourth case, twenty-four days and at the ninth week seventy days. After this period—the eighth to tenth week—and while the patient was still receiving the drug, the rate of growth became faster, returning practically to the pre-treatment rate by fourteen weeks. The tendency towards retardation of growth was also observed in those cases who subsequently became negative on culture.

The fact that these observations may be based on factors inherent in the technique used for culture has been carefully considered. Cultures were prepared by the trisodium phosphate method and it is possible that this might act with the P.A.S. in sputum to produce inhibition of growth. Again it is possible that there may have been an increasing concentration of P.A.S. in the sputum as treatment progressed. Even allowing that this may have occurred it seems unlikely that the degree of "contamination" of sputum with P.A.S. should diminish in all 4 cases at approximately the same stage in treatment. This might occur, however, if at this stage the metabolism of P.A.S. by the body undergoes a change. We are at present trying to elucidate these problems. It remains to be determined whether P.A.S.-fast strains of tubercle bacilli have been produced in those 4 cases, and work is proceeding to ascertain the answer to this question. The literature on drug resistance is extensive and it has been known since before the end of last century that organisms can be trained to withstand previously lethal doses of drugs, particularly if suboptimal doses of the drug are used. It is possible that the bacillus has been trained into drug-fastness by our scheme of dosage. In this connection it is

interesting to note that Vallentin (1947) used a scheme of dosage involving eight days treatment followed by eight days rest—though he gives no reason for the adoption of this course—and Erdei and Snell (1948) advise continuing treatment until P.A.S.-fast strains appear.

Finally, is there a correlation between the bacteriological changes observed and the clinical state of the patient? The observation that clinical improvement can continue uninhibited by the development of streptomycin-resistant organisms has been made by Crofton and Mitchison (1948) and others. Of the 4 patients in whom the effects upon the tubercle bacillus have been described above, two have shown definite deterioration of the lung condition during treatment though in one the general condition has been maintained, and one has shown deterioration following the cessation of treatment. One has just completed the course of treatment and no change has been observed. It is also of interest that clinical deterioration with return of the cavity to its previous size and reappearance of tubercle bacilli in the sputum also occurred in one patient about the tenth week. The tendency for the B.S.R. to rise again at this stage has also been noted.

### CONCLUSIONS

It is felt that it is undesirable to make a categorical statement on the efficacy of para-aminosalicylic acid in the treatment of pulmonary tuberculosis based upon our own limited experience with the drug. In the first place the type of case in which we have used the drug has been the very one in which chemotherapy of any type is very much at a disadvantage. In the second place our scheme of dosage may have been inadequate for the production of the maximum therapeutic effect.

Nevertheless there are three points on which emphasis must be placed. Firstly, although we have seen some striking isolated effects which can only be attributed to the action of P.A.S., the over-all impression we have obtained is that the clinical results in the type of case which we have treated with the drug have been disappointing so far as its curative effect on the tuberculous lesion is concerned. All but one of the cases treated have, however, experienced an increased sense of well-being and have shown a definite improvement in their general condition. The favourable constitutional effects of the drug have been disproportionately greater than the effects upon local lung lesions. The striking exception to this has been the case of chronic disseminating tuberculosis to which reference has already been made. It is considered that further investigation into the use of P.A.S. in this type of case is desirable. Secondly, in the dosage which we have employed we regard P.A.S. as a drug with negligible toxic effects. Thirdly, we have observed several striking effects upon the tubercle bacillus in patients treated with the drug. There is evidence to suggest that P.A.S.-resistant organisms may be produced and proof of this is

being sought. It is obviously important to determine the existence and characteristics of P.A.S.-fastness, particularly in relation to dosage and possible combination with streptomycin in the treatment of tuberculosis.

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# CLINICAL STUDY OF THE USE OF PARA-AMINO-SALICYLIC ACID IN THE TREATMENT OF PULMONARY TUBERCULOSIS

By ROSE I. L. DONALDSON, M.B., Ch.B.

*From Dumfries and Galloway Sanatorium, Lochmaben*

TEN of our patients have been given a course of three months' treatment with P.A.S.

## CHOICE OF CASES

The cases which were selected for this trial presented rather a wide variety of problems. They fall roughly into three clinical groups:—

(a) *Early*.—The two cases falling into this group were chosen despite the early nature of their lesions, one because conversion of the sputum to positive had occurred during a period of apparently mechanically effective collapse therapy, and the other following a failed pneumothorax as the patient was of Malayan nationality and might therefore be expected to present a low resistance to the tubercle bacillus.

(b) *Intermediate*.—All four cases in this group had bilateral active lesions of moderate extent.

- (i) In one an ineffective pneumothorax had been abandoned,
- (ii) in another previous bilateral pleurisy prevented collapse of the lungs in the puerperium,
- (iii) and, of the remaining two, the drug was used to control contralateral disease; during pneumothorax in one, and with a view to possible thoracoplasty in the other.

(c) *Advanced*.—In this group two patients had recent active infiltrations with cavitation, and two were the subjects of widespread disease of a broncho-pneumonic nature.

One case with recent extensive disease and considerable toxæmia originally selected exhibited complete intolerance to the drug which necessitated abandonment of the course after only one and a half days' trial. She has not been included in the results.

## THE PROBLEM OF CONTROLS

The scientific control of the effect of treatment in a series such as this, with its widely differing problems, is an ideal, possible to achieve only where a large number of cases is available to draw from. In this study the only control is an arbitrary one, *i.e.* in assessing our results an attempt has been made to estimate the actual progress achieved

A contribution to a Symposium on the Use of Para-aminosalicylic Acid in the Treatment of Tuberculosis read to the Tuberculosis Society of Scotland at a meeting held in Glasgow on 28th January 1949.

gauged against the expected progress of the disease with regard to the trend observed before treatment started.

### DOSAGE AND TOLERANCE

At the beginning of the trial, dosage as originally recommended by Herts Pharmaceuticals Ltd. was used but several patients quickly became intolerant and volunteered the information that it was the night doses which they found most upsetting. A change was therefore made to seven doses at two and a half hourly intervals during the day, making in all a total of 25 gm. per day with a weekly course of six days. On this dosage four patients still complained of nausea, vomiting and diarrhoea and with them the dosage was cut to 15 gm. per day at the same intervals. This reduced dosage was tolerated well.

Since it appeared from personal communications that the majority of our colleagues were employing the Herts Pharmaceuticals Ltd. preparation of P.A.S., we deliberately changed after a very brief period to the Ward, Blenkinsop & Co. variety. For all practical purposes, therefore, this report may be stated to be based on the latter preparation. It is one of the sodium salt of para-aminosalicylic acid.

There was no noticeable difference in either the severity or incidence of toxic effects between the drug as supplied by Herts Pharmaceuticals Ltd. and that supplied by Ward, Blenkinsop & Co.

### ESTIMATION OF BLOOD LEVELS

As regards the estimation of blood levels of P.A.S., we have experimented with four recommended methods.

(1) That originally recommended by Herts Pharmaceuticals Ltd. employing Ehrlich's reagent of para-dimethylaminobenzaldehyde dissolved in sulphuric acid.

(2) A modification of the above suggested by Klyne and Newhouse in which the para-dimethylaminobenzaldehyde is dissolved in alcohol. The principal disadvantage of these two methods is common to both in our experience, and is that the range of colours obtained is too narrow for a satisfactory calibration curve to be worked out.

(3) The third method used was that advised by Ward, Blenkinsop & Co. which employs the coupling of diazotised sulphanilic acid with an alkaline solution of P.A.S. By this method a wide range of colours is obtained but the colours, unfortunately, darken slowly on standing. However, if the absorptiometer reading is taken at a stated interval following the addition of the last reagent, this drawback can be obviated.

(4) A method which has recently been described by Klyne and Newhouse, of the London Post-graduate School of Medicine, utilising the colour change obtained when naphthylethylenediamine is coupled with a diazotised solution of P.A.S. The colour range obtained by this method is satisfactory and it has the advantage that the colours,

which are stable, are also directly proportional to the P.A.S. concentration in the blood.

Our experience has been widest with method (3) and we feel that the results obtained by this method are reasonably reliable. Method (4), however, of which our experience is shorter, has certain advantages—notably that a very much smaller quantity of blood is required, and the figures obtained would appear to be equally accurate. It is possible that this method will prove to be the most generally useful.

As regards urine estimations—these we have abandoned as the concentration would seem to vary with so many factors and the estimations appear, therefore, to have little clinical value.

### RESULTS OF TREATMENT

It would be impossible in the time available to give in detail the results we have obtained in all our patients and we have, therefore, drawn up a table in which we have attempted to summarise the position for each patient.

Cases.	Daily Dose (gm.).	Blood Level (mgm. %).	Results of Treatment.					
			Clinical.	X-ray.	T.B.	B.S.R.	T.T.	Prognosis.
Early . . }	1 15	4.4	No change	Improved	+ + +	6 → 6	Increased	No change
	2 25	6.0	Improved	Improved	+ +	29 → 5	Increased	No change
Intermediate }	3 25	7.0	Improved	Improved	— →	23 → 8	Increased	Improved
	4 25	6.0	Improved	Improved	+ →	43 → 6	Increased	No change
	5 25	6.0	Improved	Improved	— →	6 → 3	Decreased	No change
	6 15	4.0	No change	Improved	+ + +	12 → 5	I.S.Q.	No change
Advanced . }	7 15	4.0	Improved	Improved	+ + + + +	76 → 36	Decreased	No change
	8 15	3.5	Improved	Improved	+ + + + *	76 → 26	Increased	No change
	9 25	5.5	Improved	Improved	+ + + *	52 → 14	Increased	Improved
	10 25	6.2	Deteriorated	Deteriorated	+ + + + *	60 → 78	Increased	No change

### DISCUSSION OF TABLE

*Blood Level.*—The average obtained throughout treatment in mgm. per cent. as estimated by the Ward, Blenkinsop & Co. method. Although the numbers are, of course, too small in our series, a scrutiny of the table shows that the degree of response to the treatment and the amount of resultant improvement would not seem to be strikingly related to the dosage given and the blood level obtained.

*Clinical.*—In this column local and systemic changes, such as physical signs, weight, temperature disturbance, etc., have been summarised. Gradations of improvement were difficult to represent in summary form, but in none has the improvement, although appreciable, been spectacular.

*X-ray.*—Improvement in the radiological appearances embraces changes such as resolution, cicatrization and cavity closure. Again the changes have not been spectacular but careful consideration of the X-ray pictures has led us to the conclusions summarised here.

*T.B.*—\* Tubercle bacilli only demonstrable on culture.

*B.S.R.*—A striking feature here, as in other reported work, is the marked fall in the reading where the initial rate is accelerated. No adequate explanation can be put forward for this finding.

*T.T.*—Serial Mantoux testing was carried out before treatment began and again following completion of the course. Sensitivity was increased to a varying extent



in the majority of cases. The significance of this finding is difficult to assess as fluctuation in the skin response to tuberculin is known to occur in the course of the disease in tuberculosis. It is, however, an interesting observation requiring further elucidation.

*Prognosis.*—In relation to each case we have tried to determine whether or not the prognosis has been materially altered by the course of treatment. Once again, nothing of a spectacular nature has emerged. Although clinical and radiological improvement may have taken place in any one patient, in only two can we say that we have materially altered the prognosis.

## CONCLUSIONS

The vital question to be answered when investigating the effect of any therapeutic agent is whether the prognosis is altered favourably and permanently whilst fulfilling the experimental criteria of Feldman and Hinshaw. These were, that there should be :—

- (a) Satisfactory tolerance.
- (b) A reversal of the disease to the non-progressive state.
- (c) Eradication of virulent infection.
- (d) Results achieved in a reasonable period of time.

Judged by these standards, P.A.S. has not in our hands proved a therapeutic agent of the first importance in that in only two cases, as noted above, are we convinced that we have materially improved the prognosis. Although the progress of the disease has undoubtedly been stayed in some of the advanced cases, permanent alteration of the prognosis cannot be claimed. It may be, however, that a more prolonged course would be desirable and further work will be required before the place of this drug in the treatment of tuberculosis can be accurately assessed.

## APPENDIX

CASE 1.—F. C. A young woman of 26 in whom collapse therapy for eight months had failed to produce quiescence of early lesions. Following three months' treatment with P.A.S., cavity closure occurred and the absence of tubercle bacilli in the sputum was confirmed by culture.

CASE 2.—A. J. A young woman aged 21 of Malayan nationality who had bilateral lesions and a previously failed pneumothorax. Treatment produced considerable improvement in X-ray appearances, in general condition; and gastric lavage, positive for tubercle bacilli at the commencement of treatment, became negative on culture.

In both these cases, however, it was impossible to be certain how much of the improvement noted was attributable to the drug.

CASE 3.—R. W. A young man of 19 who had bilateral active disease with unilateral cavitation. A pneumothorax induced for control of the lesion with excavation had to be abandoned because of broad adherence. Treatment with P.A.S. has resulted in cavity closure (confirmed by tomography), but the most striking change in this patient is the improvement in the general condition and mental state in a patient previously apprehensive and with a fear of the needle.

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	cystine .. ..	0.3 %	1.0 %
	methionine .. ..	0.5 %	1.6 %
	threonine .. ..	1.2 %	4.0 %
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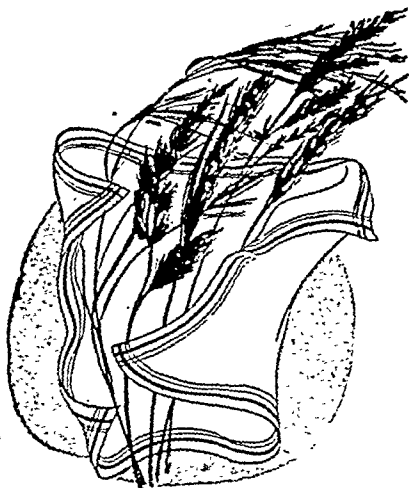
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CASE 4.—A. P. A woman of 29 in which the treatment of bilateral active lesions in the puerperium gave rise to some anxiety as bilateral collapse therapy was unlikely to succeed owing to previous bilateral pleurisies. Following a course of treatment with P.A.S. her condition has improved sufficiently to allow of her discharge and a confident hope that the lesions are now quiescent. A previously positive gastric lavage result has converted to negative on culture.

CASE 5.—N. McK. A woman of 27 in whom the drug was used to control contralateral disease during pneumothorax treatment of the other lung.

CASE 6.—T. G. A woman of 29 with bilateral lesions. Cavitation was present on one side for which ultimate thoracoplasty was being considered but gradual deterioration over a period of months of recent infiltrations on the contralateral side was giving cause for concern. Treatment with P.A.S. has resulted in a cessation of this downward process.

CASE 7.—A. W. A woman of 28 with bilateral active disease and cavitation. Poor general condition. Treatment has resulted in little change in general condition. Deterioration in the X-ray appearances, which had been taking place rapidly before treatment, was stopped and some resolution has resulted. The disease is still, however, active and extensive.

CASE 8.—J. L. A young woman of 20 with recent bilateral disease with cavitation. Treatment resulted in improvement in general condition and feeling of well-being. Some resolution has occurred in the infiltrations with a moderate reduction in cavitation. It is possible that this case will be brought within the bounds of collapse therapy. Tubercle bacilli previously present in the sputum in large numbers can only now be demonstrated by gastric lavage.

CASE 9.—N. M. A girl of 16 with widespread bilateral involvement of recent origin and without cavitation. Resolution of the lesions has taken place steadily and continuously during treatment; more rapidly, it is considered, than could have been expected on bed rest alone. Complete quiescence has not yet been achieved as tubercle bacilli are still present on gastric lavage although only demonstrable by culture.

CASE 10.—D. McM. A man of 43 in whom a recent broncho-pneumonic dissemination had taken place following hæmoptyses. Considerable toxæmia was present. Despite slight initial improvement, deterioration took place both systemically and locally, and it would appear that the expected course of the disease was not materially altered despite a reasonably satisfactory tolerance to the drug. It is interesting to note in this patient, however, that tubercle bacilli previously abundantly present in the sputum could only latterly be demonstrated on culture.

# TREATMENT OF TUBERCULOUS EMPYÆMA WITH P.A.S.

By Dr J. SIMPSON

*From Ruchill Hospital, Glasgow*

THIS is a short report on twelve cases of tuberculous empyæma treated with P.A.S. in Ruchill Sanatorium between January and December 1948. This comprises all cases of tuberculous empyæma admitted to Ruchill during that year. No attempt was made to treat alternate cases by aspiration alone or by aspiration and drugs. This series is uncontrolled.

## TECHNIQUE

The method of treatment was to empty the empyæma cavity of pus by aspiration, after preliminary screening, and then to inject P.A.S. into the space. This was done at weekly intervals, unless the pus was seen to be absent or minimal on screening. Treatment was continued until the fluid in the empyæma cavity became clear or the space obliterated. When the fluid became clear, aspiration was continued but no P.A.S. was injected.

The preparation of P.A.S. used was a 20 per cent. solution sodium salt in sterile water. This was supplied in 10 ml. ampoules. One ampoule of this solution, *i.e.* 2 gm. of P.A.S., was injected into the empyæma cavity at each treatment.

## BACTERIOLOGY

The pus was examined for the presence of the tubercle bacillus by direct smear only. In four of the twelve cases the tubercle bacillus was demonstrated in the direct smear. In these four cases after treatment with P.A.S. for a variable period (one to two months) no tubercle bacilli were present on the direct smear.

## TOXICITY

No toxic effects attributable to P.A.S. therapy were observed in this series. In two cases transient bloodstaining of the pleural fluid was noted, but this was considered to be due to accidental puncture of a vessel in the parietal pleura, as the blood soon disappeared and further staining did not occur during continuance of P.A.S. treatment.

## RESULTS

The results of treatment briefly are as follows :—

In one case only was complete re-expansion of the lung secured with no residual fluid in the pleural cavity. This was in a young woman of 22 who developed a pyopneumothorax following adhesion

Given to the Tuberculosis Society of Scotland as part of a symposium on P.A.S.

section in September 1947. She was treated with P.A.S. from February to March 1948. By May 1948 the affected lung had completely re-expanded and there was no residual fluid in the pleural space.

In three cases treatment has been reasonably successful in that almost complete re-expansion of the lung has been secured with only a small amount of clear fluid with no tubercle bacilli present on the direct smear. One of these three cases was a girl of 17 who developed an empyæma following adhesion section in June 1947. She was treated with P.A.S. from February to July 1948.

In seven cases an empyæma cavity with thick walls producing variable amounts of pus has persisted. One of these cases was a young woman of 25 who developed a pleural effusion following thoracascopy in June 1947. The fluid was aspirated, but finally went on to become an empyæma. She has been treated with P.A.S. from February 1948 to date, but there is still an empyæma cavity.

The remaining case had a fatal outcome. This was a girl of 14 with extensive bilateral pulmonary tuberculosis who was admitted with a spontaneous pneumothorax and a hæmorrhagic purulent effusion. She received P.A.S. therapy for five weeks. She developed a sinus in the chest wall and a frank hæmothorax which was treated by aspiration only. She died of an abrupt fatal hæmorrhage into her pleural cavity.

In all cases it was found that weekly aspiration and injection of P.A.S. into the empyæma space in a variable period of time resulted in a thinning of the pus. Whether this was due to P.A.S. or simply to aspiration is largely debatable, as many of you will be able to record cases where by simple aspiration this occurred.

It would be unwise to draw conclusions from this small uncontrolled series and I shall not attempt to do so.

(Dr Simpson illustrated his cases by showing numerous X-ray films.)

## REPORT ON CASES TREATED WITH P.A.S. AT ROBROYSTON HOSPITAL, GLASGOW

By W. B. SUMMERS, M.B., Ch.B.

ORAL P.A.S. was first used in this hospital in the month of June 1948. This summary covers the period June to September 1948.

The para-aminosalicylic acid was supplied by Herts Pharmaceuticals Ltd., the sodium salt being freshly prepared each day by neutralising the acid with the molecular equivalent of analar sodium hydroxide or analar sodium bicarbonate. The pH of each batch was adjusted to 6.8.

The dosage given was 23 gm. in the twenty-four hours for six days each week. Blood levels averaged 8.11 mgm. per cent.

Nine cases of pulmonary tuberculosis were treated during this period, of whom four were the fibro-caseous type and three exudative—the remaining two were tuberculous empyemata, and their oral P.A.S. was supplemented by intrapleural injections of paramisal sodium.

In none of these cases was any improvement observed during treatment. The Scandanavian workers and Dempsey and Logg had reported an early fall in temperature and E.S.R. accompanied by an improvement in the general condition of the patient, later followed by a fall in pulse rate, and a rise in the hæmoglobin content of the blood. In none of our cases were these effects observed and radiologically there was no evidence of improvement.

It had been intended that each patient should have at least a three months' course of treatment, but on account of various toxic symptoms, the drug had to be withdrawn, either temporarily or permanently in every case. These toxic effects were:—

(1) *Nausea*.—This symptom occurred in every case at some period during treatment. It usually appeared from one-half to one hour after administration.

(2) *Vomiting*.—This occurred in six cases, in four of whom it became so frequent that the drug had to be withdrawn.

(3) *Œdema and Albuminuria*.—Occurred in two cases. The onset was sudden, and when the drug was withdrawn, the signs gradually cleared over a period of fourteen days. In one of these two cases œdema and albuminuria reappeared when the drug was once more administered.

(4) *Cardiac Arrhythmia* was noted in three cases and took the form of frequent extra systoles, which in two cases progressed to coupling. Within twenty-four hours of stopping the drug, the rhythm became regular again.

In addition to these well-defined side effects, there were four cases who complained of pain, stiffness and some loss of power in certain

muscle groups. The muscles affected were those of the neck and shoulder girdle, and to a lesser extent the upper and lower limbs. These symptoms gradually cleared when the drug was withdrawn.

Naturally the occurrence of these side effects made us suspect the presence of some toxic impurity in the drug. However, detailed chemical and spectroscopic analysis of samples of (a) the drug as supplied by Herts Pharmaceuticals Ltd., and (b) the sodium salt solution prepared in the hospital, revealed only minute traces of meta-aminophenol in the latter.

By this time, supplies of the crystalline sodium salt were becoming available, and the next group of cases which Dr Bankier is about to describe were treated with this preparation of the drug.



## REPORT OF CASES TREATED WITH P.A.S. AT ROBROYSTON HOSPITAL, GLASGOW

By J. D. H. BANKIER, L.R.C.P., L.R.C.S. Ed., L.R.F.P.S. Glas.

YOU have heard from Dr Summers something of our experiences in using the sodium salt prepared in the hospital, from free acid, and I need hardly add that we were rather disappointed in the results obtained and more than a little worried over the toxic side-effects encountered.

However, the sodium salt became available from the manufacturers, and it was decided that the drug should have a further trial in its new form, and that some of the patients previously showing intolerance should be included in the series. Since the middle of November, seven patients have had the drug for periods of from six to ten weeks, and have exhibited no toxic signs apart from occasional transient sickness and looseness of the bowels. Our dosage and method of administration (25 gm./day in 3 gm. doses) have remained unchanged and comparable blood levels have been obtained.

Of the seven cases, females between the ages of 16 and 24 were all considered at the time to be unsuitable for any form of collapse therapy. Three had pleural effusion, with active parenchymal lesions and cavitation; three had an area of massive disease pneumonic in type, and one had a relatively small, recent lesion with cavitation in one apex: in all cases, the sputum was positive.

In the pleural effusion cases, the effusion did not appear to clear up more rapidly than with bed-rest alone: the parenchymal disease appears to have become rather more firm and it has not spread appreciably, but cavitation persists.

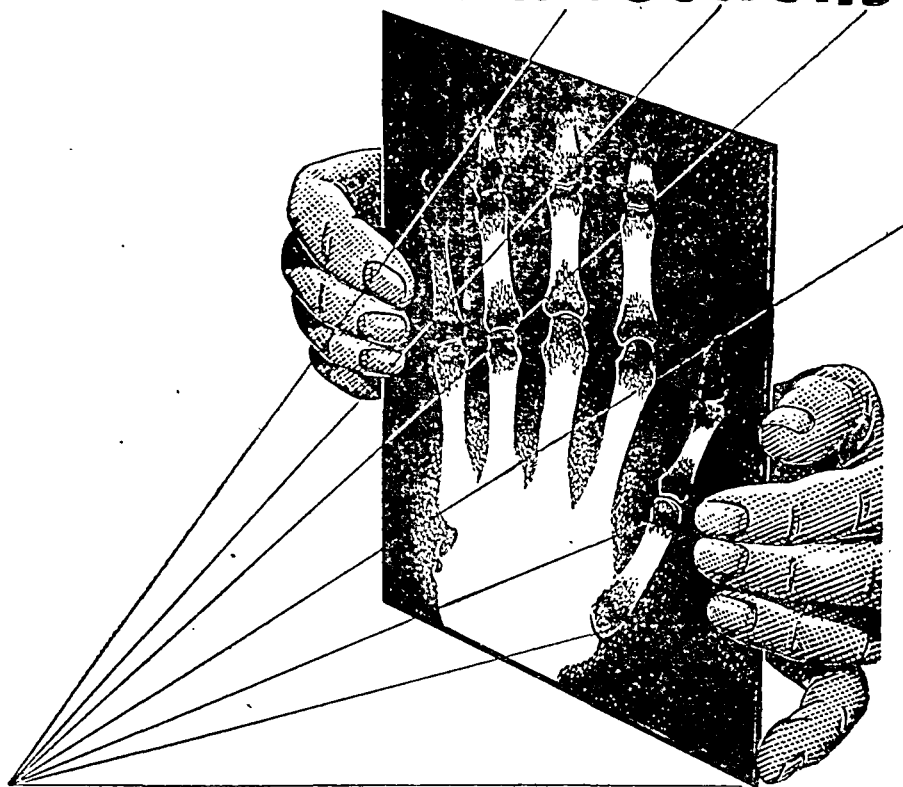
In cases with the pneumonic type of disease, no appreciable differences were noted in the grossly diseased lung, but in one case, a very early lesion in the contralateral apex has regressed.

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This series of cases is very small, and one would hesitate to draw any definite conclusions from it, and in no one case could it be said that improvement has been unequivocally due to the drug. It is also obvious that beneficial effects have occurred only in cases with small lesions, and that it has no effect at all in the presence of dense caseation.

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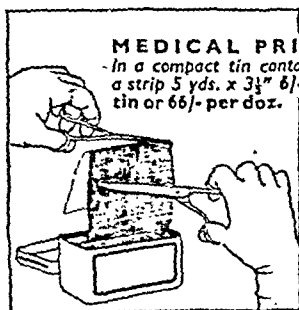
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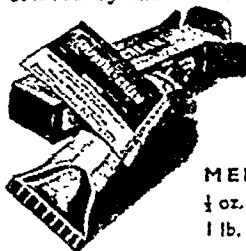
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## DEVELOPMENTS IN THE SURGERY OF THE LABYRINTH

By A. BROWNLIE SMITH, M.D., F.R.C.S.

THE history of the surgery of the labyrinth may be roughly divided into two sections, (1) the surgery of labyrinth suppuration, and (2) the surgery of the non-infected labyrinth.

The first section comprises surgical interference in cases of acute labyrinthitis, both circumscribed (as in a labyrinth fistula), and diffuse (Fig. 1). The second comprises surgical interference on the labyrinth in cases of otosclerosis, and in cases of Menière's disease. It is an interesting point, and significant of the audacity of our otological predecessors, that surgical interference on the non-infected labyrinth probably preceded, by some years, that on the infected labyrinth.

Before discussing the early history of labyrinth surgery it is important to consider the changes which have occurred in the surgery of the approach to the bony labyrinth. In the early days, a radical mastoid operation, using the retro-auricular route, was almost invariably performed. This method involved removal of the mastoid air cells, if present, opening the tympanic antrum, removing the posterior meatal wall with incus and malleus and tympanic membrane. The outer wall of the labyrinth was thus exposed. In later years, however, it was found that approach to the lateral and posterior semi-circular canals could be obtained by opening the antrum and removing the bony posterior meatal wall. This might or might not involve removal of the incus and head of the malleus, but left the tympanic membrane and the middle ear cavity intact. More recently, in some clinics, the retro-auricular route has been abandoned in favour of the trans-meatal approach by which access to the lateral semi-circular canal is obtained through the posterior wall of the auditory meatus. It is important to remember that in obtaining access to the bony labyrinth by present methods, either by the trans-meatal or retro-auricular routes, the middle ear cavity with the tympanic membrane is left intact.

In 1893, Adolph Jansen of Berlin published a description of a surgical operation on the labyrinth which was really the first serious attempt to treat the labyrinth in the human subject by surgical means. At that time, it will be remembered, the only conditions for which surgical procedures on the labyrinth were adopted were suppurative cases; surgery, in fact, was aimed not at restoring function to the labyrinth, but at draining pus. Jansen approached the labyrinth posterior to the facial nerve, after the radical mastoid operation had

A Honyman Gillespie Lecture delivered in the Royal Infirmary 1949.

been performed, and by following the posterior semi-circular canal was able to open it into the vestibule and so drain it.

In 1902, Hinsberg of Breslau, described another method of opening the labyrinth through the oval window, anterior to the facial nerve, and by means of a drill removed the bony wall of the labyrinth connecting the oval and round windows. He recommended (it is interesting to note), that the drill should be dipped occasionally into boracic solution to prevent undue heat in the drill affecting the facial nerve. The danger of facial paralysis has always been present in any operative work in this region, and any procedure which would help to eliminate this risk received attention.

In 1903, Ricardo Botey described three cases of trepanation of the labyrinth involving a slight modification of the technique of Hinsberg.

The surgical treatment of suppurative infections of the labyrinth was very fully discussed at the International Congress at Bordeaux in 1904 when the British contribution to the subject was made by Sir James Dundas Grant. But no description of any British operative work on the labyrinth appears to have been given at this Congress.

In 1905, Julien Bourguet of Toulouse described a method by which he combined opening the lateral canal with removal of the promontory as in the Hinsberg operation, leaving the facial nerve in the bridge of bone between the two openings. This appears to have been a considerable advance, as in those days, the operation was known by Bourguet, as the Bourguet-Hinsberg operation, and by Hinsberg, as the Hinsberg-Bourguet (Fig. 2).

In 1907, John D. Richards, described a more extensive labyrinth operation in which all the semi-circular canals were opened. This operation, however, appears to have been too extensive. Indeed, if one compares the relative sizes of the bony labyrinth with the pleural sac, Richard's operation would be similar to removal of half the chest wall for drainage of an empyema. About this time also, Professor Neumann of Vienna modified the original Jansen operation.

When I first became interested in labyrinth surgery twenty years ago, the Neumann operation and the Hinsberg were the recognised procedures. But all these operations were destructive in that they were performed for suppurative conditions, and the patient, if he recovered, could not expect any return of the function of the hearing or balancing apparatus.

The dangers inherent in the surgery of the labyrinth did not deter bold men from attempting interference in non-suppurative conditions, and the main problem of the otologist of the last century, as it is to-day, was the progressive deafness associated with otosclerosis. As far back as 1876, Kessel of Jena attempted to treat the disease by removal of the footplate of the stapes with the idea of replacing its footplate by a movable cicatricial membrane, but the risk of infection of the

labyrinth was very real indeed, and the technical difficulties involved, before the introduction of local anæsthesia and of the vaso-constrictors, were great. Twenty years later, in 1896, Passow, of Berlin, attempted to follow the same procedure by forming a movable membrane to replace the fixed stapes footplate and to do this he drilled into the promontory with a trephine. He succeeded in producing an improvement in the hearing but this was only transitory and the risks of infection were considerable. Very general opposition to these methods of operation on the labyrinth found expression at the Rome Congress in 1894, and at the Paris Congress in 1900, on the grounds that these methods induced the risk of fatal infection and also, even if that did not occur, there was great risk of total loss of hearing. Ten years elapsed after Passow's work before any further attempts were made to re-open the question and then Barany suggested making an opening in the posterior vertical canal. He believed that this method would prevent infection and that the improvement in the hearing would be more permanent. He did achieve success, but that success was only transitory, lasting, in fact, only a week or so. British surgeons now became interested in the operative treatment and, in 1913, Jenkins of London, operated on two patients. In one he covered the fistula with a skin graft; in the other he covered it with a small flap from the membranous meatus. But one patient became totally deaf shortly afterwards, and the other had his hearing made worse, so Jenkins abandoned the method. Jenkins was certainly the pioneer of the operation in Great Britain, and it is interesting to note that a few months ago I had occasion to write to a doctor in Annan about a patient, who, I thought, would be suitable for a fenestration operation. The doctor replied that they were rather interested in the operation there as Jenkins had retired to and died in the village.

It is safe to say that the present position of the fenestration operation is due to the interest, perseverance and tenacity with which Professor Holmgren of Stockholm pursued the question during the long period from 1917, when he first became interested in the subject, until other surgeons adopted his methods. Holmgren was attracted to the surgical possibilities of operation by his association with Barany and, in 1917, performed his first fenestration, this time on the superior canal, in the hope that the middle fossa dura would help to prevent re-growth of bone. He has assiduously studied, altered and perfected his technique during the last thirty years and is still actively engaged in the subject. To him goes the honour of keeping the fenestration flame alight until it blazed forth at the beginning of the present decade. But during the twenty years in which Holmgren was pursuing his lonely studies, other surgeons occasionally attempted the operation, and credit must also be given to Soudille of Nantes who operated in three or more stages and who did produce fairly lasting results.

On 17th June 1917, the late Dr J. S. Fraser operated on a patient in the Royal Infirmary for otosclerosis. He operated on the worse

ear, performed a radical mastoid operation, removed the bony cap of the lateral canal and covered it with a skin graft. The patient recovered from the operation, but five days later developed surgical scarlet fever and was transferred to the City Fever Hospital where she spent eleven weeks. She also appears to have developed rheumatic fever. She obtained an improvement in hearing on the operated ear and Dr Fraser demonstrated the case at a meeting of the Scottish Otological Society in 1934. In the meantime, the patient had become a chess champion, but was very deaf, while the operated ear, which had originally been the worse hearing ear, was now the better ear. It was remarked in the discussion that Dr Fraser had certainly waited a long time—seventeen years—before showing the results of his operative treatment. Shortly after operating on this case he operated on another, but the second case lost the hearing completely because of labyrinthitis. Some years later he operated on a non-infected labyrinth for tinnitus, but the patient developed meningitis and died. One must remember that no sulphonamides or penicillin were available at this time and this fatal case induced Fraser to abandon attempts at operating on a non-infected labyrinth, and it was not until 1937, as I shall explain later, that another attempt was made in Edinburgh to treat otosclerosis by this means.

In an address to the Otological section of the New York Academy of Medicine, in 1923, Fraser mentions these three cases and suggests that the dissecting microscope used by Professor Holmgren may enable us to operate on the labyrinth with greater accuracy. But Fraser did not repeat the operation, although the first patient had referred many others to him.

As far as I am aware, no other operation for this disease was performed in Edinburgh until I operated on a patient from the north of Scotland in the autumn of 1937. That summer I visited Holmgren's Clinic in the Sabbatsberg Sijkhous in Stockholm and decided to attempt the operation on my return. The operation was done in two stages; the first consisted of a modified radical mastoid operation, with removal of the incus, cutting a small flap from the posterior meatal wall and applying a skin graft to the mastoid cavity. The patient then returned home until the cavity had completely epithelialised, but it is interesting to note that after the first stage of the fenestration operation the patient obtained a remarkable temporary improvement in the hearing of the opposite ear. I have, on a number of occasions, found a temporary improvement in the hearing of the opposite ear after a successful fenestration, but, in this first case, the improvement occurred after the first stage of the two-stage fenestration operation.

On 12th November 1937, the second stage of the operation was carried out under local anæsthesia, with considerable hesitancy and some anxiety. The incision was made through the old scar, a small skin flap was raised from the prominence of the lateral canal and with a fine Holmgren's curette the bone of the lateral canal was gently

scraped away until the membranous canal could be seen. The only magnification used was a large reading glass giving a magnification of  $2\frac{1}{2}$  diameters. When the canal was opened the patient became violently giddy, was very sick, yet obtained a dramatic improvement in her hearing on the operating table, being able to hear a whisper at a distance of six feet, the previous distance being seven inches. This improvement, however, did not last, and when I saw her again in April 1938, her hearing had returned to its pre-operative level. She decided, however, to have the fenestra re-opened and, in June 1938, under general anæsthesia, I re-opened it with less hesitancy and much less anxiety. On this occasion a marked improvement in her hearing occurred. When she left for the north at the end of June she could hear a conversation voice at twenty feet with the operated ear and a whisper again at six feet. I next saw the patient on my return to civil life in 1945, and found her hearing had again deteriorated. She was anxious to try again, and in April 1947, I again re-opened the fenestra, with once more a remarkable improvement in her hearing in that she could hear a conversation voice at sixteen feet. She was naturally very thrilled at hearing again especially as she had now married, but, when I last heard from her, her hearing had again deteriorated.

Great advances have been made in the technique of the operation since these earlier days. Dr Lempert, of New York, introduced a trans-meatal approach to the lateral canal and made the fenestra with a dental burr. In this country, Dr Hall has perfected a technique using a drill, continuous irrigation and suction to remove the bone dust and also making the actual fenestration with the aid of an operating microscope. In 1920, at an International Congress in Paris, Holmgren described his technique of using a Zeiss Gullstrand binocular magnifier, giving a magnification of approximately 3 diameters, and also a Zeiss binocular microscope with a magnification of 10 diameters. The latter, however, was used mainly for inspection purposes as the working distance of the microscope was much too short. Hall, however, using a Reichart single objective binocular microscope of long working distance was able to use the instrument as an operating microscope, and his technique is now the established one in many of the clinics in this country. After the recent war, microscopes were almost unobtainable but now there are at least three twin objective binocular microscopes specially made for the fenestration operation. The microscope must have an adequate projection lighting system incorporated and the ocular system, working at a distance of approximately nine inches from the object, should have a good depth of focus with a fairly wide field. For a time I used a Beck microscope which I adapted for the purpose, but now I find the microscope made by Cooke of York more satisfactory.



## THE PRESENT POSITION OF LABYRINTHINE SURGERY

At the present day, operative work on the labyrinth is largely confined to non-infective diseases of the labyrinth. Before the introduction of penicillin and the sulphonamides, acute infective conditions of the labyrinth were potentially dangerous and required opening and draining of the labyrinth by the Neumann or Hinsberg method. Even in performing the radical mastoid operation in the presence of a dead labyrinth (as a result of recent acute labyrinthitis), the risk of lighting up a latent labyrinthine infection was great, and Fraser invariably in these cases opened the lateral semi-circular canal as a precautionary measure. Also, in cases of circumscribed labyrinthitis (when a small portion of the bony wall of the labyrinth had been eroded by disease), the radical mastoid operation frequently broke down the fine barrier and the circumscribed labyrinthitis became diffuse with the risk of meningitis arising. To obviate this, the labyrinth was opened at the time of the radical mastoid operation, resulting, of course, in total deafness in the operated ear. At the present time by the prophylactic use of penicillin and of the sulphonamides, operation on the infected labyrinth is comparatively rare. Even in the presence of a labyrinthine fistula with a circumscribed labyrinthitis, penicillin prophylaxis usually prevents the development of a diffuse labyrinthitis, and some hearing is often preserved in the infected ear.

To-day, then, operative work on the labyrinth is mainly confined to the treatment of two diseases, (1) progressive middle-ear deafness, resulting from otosclerosis, and (2) Menière's disease.

(1) *Operative Treatment of Otosclerosis*.—As I have already said, the pioneer work of Gunnar Holmgren and the perfection of technique which has resulted from the use of the operating microscope, dental drill and the continuous irrigation and suction apparatus has made the fenestration operation extremely popular. The risk to life is small, the risk of total loss of hearing is slight, and the chance of at least temporary improvement in hearing is great. In my own series of 64 operations there has been one death. After a successful operation lasting one hour and fifty minutes, the sixty-fourth case died fifteen minutes after he had returned to bed and post-mortem examination showed an unexplained massive collapse of the lungs; no case lost the hearing completely; two cases developed otitis media which rapidly resolved under penicillin therapy with no deterioration of the hearing; one case developed facial paralysis seven days after the operation, but this completely cleared up in three weeks, while another developed a paralysis immediately after the operation, probably as a result of undue heat from the drill, which completely resolved in four months. Of the 64 operations, 46 showed improvement of varying degree in the few months following the operation—the improvement ranging from slight to complete rehabilitation for ordinary conversation. But a proportion of cases lose the improvement in the

hearing as a result of the closure of the fenestra, and even when the fenestra remains open some deterioration of the hearing may occur. Various attempts have been made by different surgeons to prevent this closure. Holmgren has tried the introduction of radium, of gold leaf, of periosteum; Lempert has altered the position of the fenestra from the prominence of the lateral canal to the dome of the vestibule and has tried the insertion of a cartilage stopple and of burnishing the edge of the opening with fine lead; Hall has perfected a technique of thinning down the bone of the labyrinth capsule and removing the bone of the actual fenestra in one piece so preventing the development of tiny slivers of bone and of bone dust which may initiate bony closure. But in spite of all these methods, bony closure of the fenestra, though not so frequent to-day still occurs in a high percentage of cases, and one of the most depressing things in fenestration surgery is to find a patient, who has obtained a dramatic improvement in the hearing as a result of the operation, gradually, sometimes in four, five or six months, lose all the improvement which has been gained. The problem of preventing regeneration of bone at the edges of the fenestra occupies the minds of otologists the world over, but it would appear from the changes in technique which are continually occurring that the solution has not yet been found. For some years it has occurred to me that the fixing of a small window frame in the fenestra might prevent closure, and I have attempted to find a small natural opening in some bone—a small opening which could be excised and fitted into the fenestra in the labyrinth. For a time I thought of excising the small opening through which the nutrient artery of a long bone enters the medulla, but it occurred to me that a more suitable window frame was obtainable in the mastoid portion of the temporal bone itself. Eighty per cent. of all mastoid processes are cellular and, in obtaining access to the outer wall of the labyrinth by the post-aural route, these mastoid cells have to be opened and removed. Now every mastoid cell connects with its neighbour and the bony walls of the cells largely consist of a very thin plate of bone. In this thin plate of bone there is the opening by which one cell connects with its neighbour and the openings are really very small but vary greatly in size (Fig. 3). It occurred to me that if one could, under the microscope, excise one of these small openings and fit it into the opening of the labyrinth it might be possible by that means to obtain bony fusion of the small piece of bone, the bone graft, to the edges of the fenestra, and so leave a prepared natural opening in the centre. The chance of survival of this small piece of bone appeared to me to be considerable, as the bone would be removed from an area little more than half an inch from where it would be placed, it would be nourished from the perilymph which was filling the labyrinth, and also it would gain further nourishment from the small meatal flap covering the fenestra. To procure this small piece of bone, all the bone chips which are removed during the approach to the tympanic antrum through the mastoid process are

preserved in saline. After the first stage of the operation is completed, and before the fenestra is made in the labyrinth, these small bone chips are examined under the microscope, and when a suitable piece is obtained, an attempt is made with the dental burr and fine forceps to excise a portion, approximately 4 or 5 mm. by 2 or 3 mm. with a small natural opening in the centre. The difficulty of preparing such a piece of bone is considerable as I have, on more than one occasion, found it to split right through just as it was almost completely excised. Also, it is very small, difficult to see, difficult to hold and extremely easy to lose. To prevent this, it is desirable to thread a fine nylon suture through the opening in the bone until it is actually placed over the fenestra. I have, however, been able to fix this small bone graft into place in one patient who has done very well indeed. She has shown the usual improvement one expects in the early post-operative stage and the cavity has healed normally. I have naturally been anxious to know if the small bone graft will remain alive and I have had some radiographs made in an attempt to demonstrate it. But demonstration of a fenestra in the labyrinth by X-rays is extremely difficult, and it is almost impossible to make out the small bone graft. I am assured, however, by the radiologist, that the fact that the bony fragment is hardly visible is a good sign and tends to show that the bone is still alive. Had the graft died, it would have shown as a small sequestrum. One hopes that the graft will become firmly united to the edges of the fenestra and that the new bone formed from the edge of the fenestra will not encroach on the small central opening. In other words, it is an attempt to graft a new oval window into the bony wall of the labyrinth. The method would appear to be biologically sound, but it will require some years before one knows if the new oval window will remain as a mobile membrane in the wall of the labyrinth. Also, as the ætiology of otosclerosis is not clearly known, the disease may still progress even when a successful fenestration has been performed and when the fenestra has remained open. I have formed the impression from my own cases, that while a successful result from the fenestration operation is more often obtained in the early age group, restoration of hearing is likely to be more permanent in the later age group. It is possible that the natural regenerative power of bone is greater in young people and that the fenestra is more likely to close in young people than in older ones. It will be interesting to see if the grafting of a new oval window will prolong the improvement in the hearing obtained after a successful fenestration. The fenestration operation is certainly the only method by which natural hearing can be restored in clinical otosclerosis, and, even if the disease progresses, the longer two mobile windows remain in the bony wall of the labyrinth, the longer the restored hearing is likely to remain.

(2) *Operative Treatment of Menière's Disease.*—Menière's disease is the other important affliction which has come within the province of the surgery of the labyrinth. While the ætiology of the disease



FIG. 1. — Diffuse Suppurative Labyrinthitis. Transverse section of the lateral semi-circular canal showing a purulent exudate in the peri-lymphatic space and a serous exudate in the distorted membranous canal.  $\times 50$ .

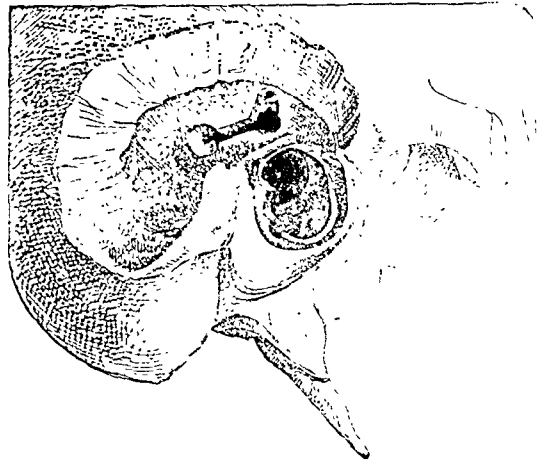


FIG. 2. — The Hinsberg-Bourguet Operation on the Labyrinth. The facial nerve lies in the bridge of bone between the two drill openings in the lateral canal and the large opening which has been made in the medial wall of the tympanic cavity.



FIG. 3. — Vertical section of the mastoid process. The mastoid cells are largely filled by œdematous mucosa but the bony trabeculae are seen with the small holes connecting the cells.  $\times 7$ .



FIG. 4. — Membranous Lateral Semi-circular Canal removed at operation. The wide and dark portion is the ampullary end of the canal.



is still obscure, pathological changes in the inner ear have been demonstrated by Hallpike and Cairns. For many years the treatment of the condition was almost entirely medical and consisted in the administration of sedatives, with dietary restrictions, while before the recent War, surgical treatment was carried out mainly by the neurosurgeons. At an early stage in the disease, although the vertiginous attacks may be frequent, hearing is usually only slightly diminished, and, in an attempt to preserve the hearing, section of the vestibular division of the acoustic nerve was the recognised surgical procedure. But, as the hearing which was preserved by this operation was often of little value to the patient, this operation has given place to direct interference with the membranous labyrinth, even although this results in complete loss of hearing in the affected ear. One important symptom is the acute mental tension which is induced in this disease, and, if the patient's occupation is one in which the development of an acute vertiginous attack might lead to a serious accident, then indeed his state is a miserable one. In a recent case, the patient was a shipwright at Leith Docks, and the thought of the onset of a sudden giddy attack at his work made him a nervous wreck. In fact, I was informed that another worker had been detailed to watch the patient continuously should the work be at all hazardous. While the modern medical treatment of the disease by means of histamine and nicotinic acid can be extremely effective, and should be given a thorough trial, there are cases—as in the patient whom I mentioned—where destruction of the reacting portion of the vestibular labyrinth is justified, even in the presence of good hearing. The shipwright had his membranous labyrinth removed with complete cessation of his giddy attacks, while the change in his mental tension was remarkable.

Destruction of the membranous labyrinth can be carried out either by the injection of alcohol into the labyrinth, or by actual removal of the membranous labyrinth, as described by Cawthorne. Alcohol may be injected either directly through the tympanic membrane and oval window or through an opening made into the lateral canal, as in the fenestration operation. The latter operation is relatively safe. It involves a conservative mastoid operation in which the antrum is opened by the post-aural route, the lateral canal opened by the burr, or a fine chisel, the endolymph sucked out and a few drops of absolute alcohol injected. The mastoid wound is then closed completely. I have one patient, an old blind lady aged 87, who decided to have the operation done at the age of 84 because she was completely bedridden and told her family doctor that her life was not worth living in her state of continual giddiness. She made a complete and speedy recovery and was able to return home in less than a fortnight, the only worry she gave being due to the pentothal she had while having the stitches removed. She can now sit at the fire quite comfortably and listen to the wireless, but she has an interesting development, as, after she has been sitting in a room for some time, she finds it difficult to reach the

door. Being blind she has to some extent lost her sense of position in space. But I have felt that there is greater risk of injury to the facial nerve from the injection of alcohol than there is from removal of the membranous labyrinth as there are some small channels through which excess of alcohol can escape if too much should be injected. Manual removal of the membranous labyrinth can be accomplished by making a slightly larger opening into the lateral canal than that required for the injection of alcohol and extracting the labyrinth by a fine forceps or probe. Fig. 4 shows the membranous lateral semi-circular canal of a patient with Menière's disease who had the condition treated by removal. He had responded fairly well to medical treatment by histamine but the attacks had not completely ceased and he was in danger of losing his job. As I said earlier, the anticipation of a sudden vertiginous attack leads to serious nervous disturbance and this patient was willing to sacrifice the little hearing he had if his attacks could be stopped for good. As there was no evidence that any of his trouble was arising from the other ear I decided that destruction of the labyrinth was justified. This was found to be so and he has now returned to work. Notwithstanding the success of this technique we have to realise that increasingly good results appear to be obtained by the new medical treatments, and one hesitates to destroy a labyrinth in the presence of good hearing unless, as in the case described, the uncertain success of treatment makes it desirable. It may yet be possible to operate within the bony labyrinth itself and probably excise or destroy only the reacting part of the membranous labyrinth without injury to the hearing, but so far it would appear that in any intralabyrinthine manipulations the auditory function is more susceptible to injury than the vestibular one. The balancing apparatus would appear to be more robust than the hearing one.

In any surgical procedure on the labyrinth, and especially if any attempt is made to carry out any work inside the bony labyrinth, it is extremely important to have delicate instruments. In working under a magnification of 8 or 10 diameters even the finest probe appears blunt, and the finest forceps crude. I have always hesitated to make the points of the probes any finer as I have felt that these instruments are made as fine as the makers think the metal will stand. In fact, a colleague of mine in another city had, under the microscope, made the point of one of his instruments very fine and found, on attempting to remove the bony roof of the ampulla, that a piece of the metal broke off and fell into the labyrinth. He could not recover it, but the patient made a complete recovery with a marked improvement in the hearing. Such accidents as these are unpleasant, and I feel that we now require in the development of the surgery of the labyrinth a number of delicately made instruments, microscopically accurate and of microscopic finish. I have no doubt that, in time, the instrument makers will produce these instruments for the otologist as they have already done for the oculist.

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## NEW BOOKS

*Cardiology.* By WILLIAM EVANS. Pp. xi+310, with 269 illustrations and 15 tables. London: Butterworth & Co. 1948. Price 35s. net.

It is explained in the preface that this book does not aim at exhaustive discussions of all cardiovascular disorders, but is based on a series of post-graduate lectures at the London Hospital. Nevertheless there is compressed into the compass of a volume of reasonable size a wonderfully broad account of such diseases. The book bears throughout the stamp of the author's well-known individuality and brings together much work previously published in scattered papers, *e.g.* on auricular tachycardia, phonocardiography, funnel-breast, the œsophagus in the radiology of the heart and vessels, and on digitalisation. Many of the views are individual and some may arouse condemnation (*e.g.* the summary dismissal of heparin in two lines as not justified, p. 302); others are unorthodox but provoke reconsideration of views long held as final (*e.g.* the definition of mitral stenosis as a comprehensive disease, p. 28, and the demolition of mitral incompetence as a clinical entity, p. 35). Certain of Dr Evans' points command the whole-hearted acquiescence of the reviewer, those on unwarranted cardiac invalidism, the management and employment of cardiac patients, and many others. It is particularly refreshing to meet in print the "self-catechism" of auscultation, which tallies closely with the method taught by a most respected clinical teacher in this school twenty-five years ago and still taught by his old pupils.

The manner in which radiology has become an integral part of a cardiac examination and the immense value of its findings, are abundantly clear from the text. In this book clinical observation of an exact type, radiology and electrocardiography are woven into a comprehensive fabric of diagnostic method.

The format, printing and reproductions are of a very high standard, the radiograms particularly showing detail with clarity.

As a survey of present-day teaching on cardiovascular disease the book has much to offer not only to the student of cardiology but to the general physician.

*Vascular Disease in Clinical Practice.* By I. S. WRIGHT. Pp. 514, with 104 figures. Chicago: Year Book Publishers Inc. 1948. Price \$7.50 net.

In this country the field of vascular disease has long been neglected by physicians, and even by many cardiologists, whose preoccupation with the arterial pump seems to blind them to peripheral events and processes. Our surgical colleagues have maintained their interest in the vessels, since it is to them that most cases of occlusive disease are referred.

The present volume comes as a welcome reminder that vascular diseases constitute a significantly large and highly interesting field in medical practice. Much of its value lies in the emphasis placed on exact diagnosis by simple methods of examination. Laboratory methods are described for completeness, but methods of clinical bedside investigation are admirably detailed.

Drawing from an extensive clinical experience, Dr Wright deals not only with the occlusive diseases of large vessels (arteriosclerosis and thromboangitis) and with aneurysms and arterio-venous shunts, but discusses disorders of vascular function Raynaud's disease, scleroderma, acrocyanosis and erythromelalgia (now "erythromalgia"). The vascular responses to cold and immersion are described, chilblains, frostbite, trench- and immersion-foot. Pariarteritis nodosa with temporal arteritis receive due notice. There is a chapter on the various shoulder-girdle syndromes formerly attributed to cervical rib. An extensive section of the book is devoted to diseases of the veins, with full discussion of modern views on the prevention and treatment of thrombophlebitis. There is similarly a section on lymphatic diseases. The author's use of dicoumarol, over long periods and apparently with safety, in the prevention of recurrent emboli in rheumatic and other cardiac cases is noteworthy.

Though one or two sections fall short of the general high standard (for example, those on aneurysms and on erythema nodosum) the book as a whole is very complete

and worthy of study by all engaged in clinical practice—whether surgeon, physician or general practitioner. The illustrations, which include several colour photographs, are of high quality.

*Unipolar Lead Electrocardiography.* By E. GOLDBERGER. Pp. 182 with 88 figures. London: Henry Kimpton. 1947. Price 20s. net.

From the nature of the instrument, an electrocardiograph records the potential difference between the points to which it is connected. In a tracing by one of the standard Einthoven leads, we have a record of the variations throughout the cardiac cycle of the algebraic sum of the potentials of the two limbs to which the electrodes are applied. For many years these leads served well enough, and for the diagnosis of all but a few arrhythmias they still suffice. For closer analysis of the ventricular complex, however, precordial leads were introduced by Wilson nearly twenty years ago. In these, one electrode is placed on the chest, over the heart, and the other on a limb. It was soon apparent that though the potential variations of the precordial electrode were far greater than those of the limb electrode, the latter were by no means negligible and introduced a serious error in the curves. To obtain curves which reflect the potential of the chest electrode alone, the other must be connected to a point whose potential varies little if at all during the cardiac cycle. Such leads, introduced in 1934, are termed "unipolar" and their use is current practice in many centres in this country and the U.S.A.

The book under review, by one who has worked intensively in this field and who has made considerable contribution to our knowledge, is one of fundamental importance to all interested in electrocardiography.

After reviewing the present state of our knowledge of the polarisation of cell membranes and the genesis of action currents, the author discusses the theory of bipolar and unipolar leads. A large part of the work is very properly devoted to the curves from normal hearts and the effects on the tracings of varying positions of the heart. There follows a full analysis of the unipolar lead curves recorded in various pathological states, hypertrophy of one or other ventricle, bundle-branch block, infarct, etc.

Though it deals with a somewhat difficult subject, the text is lucid and easy to follow. Throughout the author returns consistently to first principles in explaining the genesis of various types of curve. It is to this logical approach that much of the clarity of the text is due.

The book is recommended as a *vade mecum* to all those engaged in this field of study.

*Textbook of Chiropody.* By MARGARET J. MCKENZIE SWANSON, B.LITT., F.C.H.S. Pp. 208, with 168 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 20s.

This admirable book, produced by the co-founder of the Edinburgh Foot Clinic and School of Chiropody, should be invaluable to the student or practitioner of chiropody and should also prove useful to general practitioners or workers in any out-patient department where variety of foot conditions is encountered. The text is well written and lucid and the many illustrations, which are mostly photographs, are clear and informative. The final chapters on clinical procedures and padding and strapping should prove especially useful to those who have had no expert training in this important branch of surgery.

*The Skull, Sinuses and Mastoids.* By BARTON R. YOUNG. Pp. 328, with 141 illustrations. Chicago: The Year Book Publishers, Inc. 1948. Price 36s.

This is one of a series of handbooks in *röntgen* diagnosis published by the Year Book Publishers. Companion volumes have already appeared dealing with the arthropathies, chest, gastro-intestinal tract, osseous system and urinary tract.

This latest publication forms a most welcome addition to the series. It presents the *röntgen* appearances of the normal skull, sinuses and mastoids at significant

stages of development from birth to adult life, their normal variants, anomalies and diseases. The author is to be congratulated on this valuable contribution to a subject which has been comparatively neglected. The third section, which deals with the mastoids, is particularly good. The illustrations are of a high standard throughout and, while the text is brief, there is a valuable bibliography. The absence of a chapter on ventriculography is disappointing, but there are few other points for criticism.

This is an excellent little book, which can be recommended to all interested in the subject.

*Treatment of Heart Disease.* By WILLIAM A. BRAMS. Pp. 195. Philadelphia: W. B. Saunders Company. 1948. Price 17s. 6d.

A deliberately dogmatic summary of the author's experience is presented for the student and general practitioner. The first section, one-third of the book, deals with pharmacology; the remainder outlining in detail the treatment of almost all cardiac conditions, contains much unnecessary repetition.

It is stated that digitalis can safely be used in all forms of congestive heart failure, no mention is made of the established danger of such therapy in "cor pulmonale."

There is little fresh knowledge to be gained from this book; clear concise statements, however, will recommend it to those unwilling to sift evidence for themselves.

*Manual of Leprosy.* By ERNEST MUIR, C.M.G., C.I.E., M.D., F.R.C.S. (EDIN.). Pp. viii+208, with 70 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 17s. 6d. net.

This "small handy book" will be valuable to physicians in this country caring for patients returned from contact with leprosy overseas as well as to workers abroad at closer grips with the disease.

Up-to-date information includes sulphone treatment and the classification adopted at the Havana conference 1948.

The description of the centripetal and centrifugal systems of control will recall to Scottish readers the elaboration of both methods in one Mission Field, at Itu and Uburu.

While over-simplification has been avoided, illustrations, cross references, extensive bibliography, adequate index and scarcity of slips add to the use and interest of this book.

*A History of the Heart and the Circulation.* By FREDERICK A. WILLIUS and THOMAS J. DRY. Pp. 456, illustrated. Philadelphia and London: W. B. Saunders Company. 1948. Price 40s.

Cardiology, or the study of the heart and circulation, is of peculiar interest to the medical historian. Conversely, almost more than in any other branch of medicine, a knowledge of history is useful and even essential to all who practise cardiology.

Drs Willius and Dry, both of the Mayo Clinic, have stimulated the reader's interest by adopting various angles of approach. The first half of the volume is devoted to a chronological account of the evolution of knowledge regarding the heart and circulation. This section consists of eight chapters and, at the end of each, there is an ample list of references to guide the reader who wishes to study the matter more deeply. The second part of the book is devoted to 21 special biographies, from Hippocrates to Sir Thomas Lewis. The third, and shortest section of the book, deals with the various subjects included in cardiology; the anatomy, the arrhythmias, the diagnostic aids, the congenital malformations, the surgery of the heart and other topics.

This welcome treatise is clearly and attractively written, and may be regarded as a most scholarly account of the progress of cardiology down the ages.

*Practical Section Cutting and Staining.* By E. C. CLAYDEN. Pp. vii+129, with 21 illustrations. London: J. & A. Churchill Ltd. 1948. Price 9s.

The author states that this book is essentially for technicians with little or no

experience, and accordingly he has gone into the details, not omitting the simplest procedure. For this very reason the book fulfils its purpose admirably. The usual methods of fixation, cutting and staining are given and, while these may vary as compared with similar procedures in different laboratories, the general details given are all sound. The illustrations are clear and helpful; one showing how a section should not appear is very useful for the beginner. This little book ought to prove very useful for junior technicians learning their work and preparing for examination, and even for those more senior the details are available for handy reference. The book is well produced, has a useful index, and can be commended for the purpose intended.

*The 1947 Year Book of Pathology and Clinical Pathology.* Edited by HOWARD T. KARSNER, M.D., HERBERT Z. LUND, M.D., and ARTHUR HAWLEY SANDFORD, M.D. Pp. 558, with 103 illustrations. Chicago: The Year Book Publishers. 1948. Price 21s. net.

This book contains selected articles from the pathological literature published during 1947. In certain instances some authors have written concise reviews of their own articles. The medical applications of radioactive isotopes are discussed at length, and although widely divergent subjects such as the sludged blood syndrome and penicillin and streptomycin sensitivity tests are included yet this book contains a complete survey of all the recent advances, with references, in the fields of pathology and clinical pathology.

*The Clinical Apprentice.* By J. M. NAISH, M.D., M.R.C.P., and J. APLEY, M.D., M.R.C.P. Pp. xi+200, with 70 illustrations. Bristol: John Wright & Sons Ltd. 1948. Price 15s. net.

This book has been planned to meet the needs of the young student passing from the orderly domain of science to the strange empirical atmosphere of the wards. It is largely concerned with methods of examination and their difficulties.

The book is divided into two parts, the first dealing with examination at leisure, the second the investigation of acute cases. It is simply and clearly written and should prove of the greatest assistance to the student beginning his hospital experience.

*Cardiography.* By WILLIAM EVANS, M.D., D.SC., F.R.C.P. Pp. ix+140, with 211 figures. London: Butterworth & Co. 1948. Price 25s.

This book deals with clinical electrocardiography and phonocardiography and replaces the author's earlier work, *A Student's Handbook of Clinical Electrocardiography*. It is planned to help those who are preparing for examinations.

An interesting feature is a series of electrocardiograms for testing the reader's knowledge. Legends are not given under these illustrations but are collected together in later pages. The section on heart sounds is particularly good and should be of the greatest assistance.

This useful book should prove extremely popular with those intending to take a higher qualification.

*Nursing Pathology.* By RAYMOND H. GOODALE, B.S., M.D. Pp. 416, with 71 illustrations. Philadelphia and London: W. B. Saunders Company. 1948. Price 15s.

No one would envy the author his task of compiling a comprehensive yet simple textbook of pathology suitable for the student nurse.

This book has sections on general pathology, applied pathology and clinical pathology and a useful glossary of terms. The section on clinical pathology is well written and should prove of value to nurses in all spheres of professional duty. The other sections are more in keeping with the standard of knowledge demanded of medical students, but sister-tutors, for whom the book will have the greatest appeal, could use them as a basis for lecture courses. The illustrations are good.

*Nursing in Tuberculosis.* By LOUISE LINCOLN CADY. Pp. vii+481, with 62 illustrations. London: W. B. Saunders Company. Price 20s. net.

This book deals with tuberculosis in all its aspects and is written by one who has a full understanding of the disease and its problems as they affect the individual and the community. It deals effectively with the practical issues of nursing, and explains briefly but clearly the pathology and epidemiology of the disease and the many surgical and medical methods of treatment which the nurse may have to carry out herself and at which she will assist. It is full of sound instruction and good advice, and the author's solicitude for the patient is everywhere evident. The integration of the hospital and health services is emphasised and chapters on psychological, social, and economic problems, and on rehabilitation are excellent.

Tuberculosis workers of all grades will find it of value. There are minor errors in places and we in this country feel that the work of the Prophit Trust demands correct spelling of its name.

*Oral and Dental Diseases.* By HUBERT H. STONES, M.D., M.D.S., F.D.S.R.C.S. (ENG.). Pp. xix+896, with 926 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 90s.

This book is excellent. It is clear, concise and well illustrated and has full references at the end of each chapter. The author avoids the tendency, so often displayed in dental textbooks, of treating dental diseases as something occurring independently from the rest of the body, both as regards cause and effect. He emphasises the fact that dental disease covers a much larger field than is often realised and much of the subject matter is therefore of interest not only to dental students and dental practitioners but also to medical practitioners.

A full description is given of recent research and this adds to the value and interest of the book. It might have been an advantage, from a student's point of view, if the author had been more definite in his conclusions as the application of research findings to clinical practice requires considerable experience.

It is not possible in the space available to refer to the book chapter by chapter, but special attention has been paid to the etiology, the histopathology and clinical features of conditions met with in the teeth and their supporting tissues, in the jaws and in the oral mucosa. Descriptions of operative procedures are necessarily brief but broad lines of treatment have been laid down.

The publishers are to be congratulated on the manner of presentation and on the excellence of the illustrations.

*The Acute Bacterial Diseases: Their Diagnosis and Treatment.* By HARRY F. DOWLING, M.D., F.A.C.P. Pp. ix+465, with 55 illustrations. London and Philadelphia: W. B. Saunders Company. 1948. Price 32s. 6d.

In his preface the author notes that the old order is changing in regard to our attitude to the acute bacterial diseases. This has occurred particularly in treatment since the introduction of the sulphonamides, penicillin, and streptomycin, but also owing to the more easily overlooked improvements in methods of laboratory diagnosis. The result has been that it is imperative to identify each disease according to its ætiological agent and this book has been written with a view to combining the new order of diagnosis with what is worth while in the old. Apart from one or two curious defects in observation such as the statement that "Peeling begins most often on the tips of the fingers or toes. . . ." in scarlet fever the author has succeeded handsomely in his subject of providing clear clinical pictures with up to date and really balanced accounts of the possibilities of treatment by the newer remedies. Those in search of a diagnosis will derive stimulus from this work although we confess to a mild scepticism in respect of the author's hope that his grouping of the conditions described will "aid the physician in narrowing the presumptive diagnosis to one group of diseases." In our judgment this is a first-class contribution to the literature of the acute infections.

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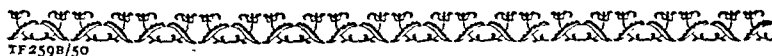
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## NEW EDITIONS

*Diseases of the Ear, Nose and Throat.* By D. G. CARRUTHERS, M.B., CH.M., F.R.A.C.S.  
Pp. 344, with 140 illustrations. Bristol: John Wright & Sons Ltd. 1948.  
Price 25s. net.

This book first published in Australia in 1943 makes its venue here as a second edition. The second edition has been reset in the light of the development and application of antibiotic chemotherapeutic agents. It is essentially practical in style and conception. The new section on penicillin and sulphonamides in otitis media is disappointing making little mention of the masking effect of these drugs. The value of the book would be enhanced by a more precise anatomical description of each region. Certain matter—lingual varix and elongated uvula are redundant.

The book can be thoroughly recommended to undergraduates.

*Gynaecological and Obstetrical Anatomy.* By C. F. V. SMOUT and F. JACOBY.  
Second Edition. Pp. xii+248, with 185 illustrations. London: Edward Arnold & Co. 1948. Price 40s.

The first edition of this book was published under the title *The Anatomy of the Female Pelvis*. The change to *Gynaecological and Obstetrical Anatomy* in this edition indicates that the authors' aim is to help in the application of anatomy to practical problems. It has further permitted the inclusion of descriptions of the placenta and the foetus in their relation to childbirth.

Large parts of the book have been re-written and much new material has been added. That function cannot be separated from structure is appreciated throughout and is especially evidenced by the inclusion of a chapter on the endocrine control of the female reproductive tract. Much information of practical use is to be found clearly described and is liberally illustrated with beautifully reproduced coloured plates, photomicrographs, photographs and diagrams.

Closer liaison might, however, still be made with the operating clinician, for example, greater anatomical detail of the lymphatic drainage of the vulva is essential for the modern extended dissection of the inguinal regions undertaken in vulvar carcinoma. Again, the anatomy involved in the operations for stress incontinence of urine could be usefully described with more precision. These are but minor criticisms of a book which is to be commended as a valuable contribution to the clinicians' library.

*Diseases Affecting the Vulva.* By ELIZABETH HUNT. Third Edition, revised.  
Pp. 211, with 36 illustrations and 19 plates in colour. London: Henry Kimpton.  
1948. Price 25s. net.

This book is written from the standpoint of the dermatologist at the request of numerous gynaecologists and general practitioners. The beautifully reproduced coloured photographs illustrating a few of the lesions met with in the author's practice greatly enhance the value of the descriptions in the text. In spite of the additional expense it would involve the inclusion of other conditions capable of illustration in this way would be appreciated in a future edition.

New material has been added especially in the sphere of therapy and, as much of the treatment described requires no special apparatus, it is well within the compass of the general practitioner. From a gynaecological standpoint, the description of the vulvar skin lesions in an acute trichomonal infection are meagre and the treatment of trichomoniasis, as well as moniliasis, could be expanded, for eradication of the primary vaginal lesion will alone relieve the vulvar discomfort. The author has, however, shown a closer liaison with the gynaecologist when discussing the confusion in the use of the terms Krausosis and leucoplakia. Arguments are advanced for their employment on a histopathological basis.

This will be found a useful volume.



*A Manual of Practical Obstetrics.* By O'DONEL BROWNE, M.B., M.A., LITT.D., F.R.C.P.I., F.R.C.O.G. Second Edition. Pp. viii+270, 218 illustrations and 8 plates. Bristol: John Wright & Sons Ltd. 1948. Price 35s. net.

This small manual is written by the present Master of the Rotunda for his students. The author is fully aware that some of the opinions expressed are not generally accepted views and he wisely advises those preparing for senior examinations not to limit their reading to this book. Also it is essentially a practical presentation of the subject and the theoretical aspects embracing ætiology and pathology are but briefly considered. Additions and alterations have been made to bring it up to date and thus present the methods employed to-day at the Rotunda.

The teaching on the diagnosis and management of cases is clear and concise and the text is illustrated with good line drawings but occasionally the rationale, wisdom and even practicability of certain procedures advocated is not always so obvious, e.g. page 120. "If this step" (traction with forceps) "fails to dilate the ring" (contraction ring above the fixed presenting part), "bring down a leg, and apply steady, prolonged traction." The treatment of eclampsia at present used in the Rotunda is described, but because of the good results produced by Tweedy when he advocated what came to be known as the Rotunda or conservative treatment the author has described this method too and in detail. The instructions given for the conduct of a trial labour are those formulated by FitzGibbon.

*Recent Advances in Obstetrics and Gynecology.* By ALECK W. BOURNE, M.B., B.CH., F.R.C.S., F.R.C.O.G., and LESLIE H. WILLIAMS, M.D., M.S., F.R.C.S., F.R.C.O.G. Seventh Edition. Pp. viii+326, with 85 illustrations. London: J. & A. Churchill Ltd. 1948. Price 21s. net.

A new edition of this book is always awaited with an anticipation that is not disappointed, for the authors have the knack of presenting their readers with facts, opinions and thoughts on the topical subjects of the day in an interesting and stimulating manner. Six chapters have been discarded from the last edition and replaced by the same number of new chapters. One of these on The Anæmias of Pregnancy is contributed by L. J. Davis. The other new subjects are Weight Change and Water Retention in Pregnancy, Lactation, Stress Incontinence of Urine, Penicillin in Obstetrics and Penicillin in Gynecology. The chapters retained have been modified so as to include fresh knowledge. Indeed those on Nutrition in Pregnancy and Fœtal Development and Erythroblastosis have practically doubled in length.

*A Short History of Ophthalmology.* By ARNOLD SORSBY. Second Edition. Pp. 103, with 6 illustrations. London: Staples Press. 1948. Price 8s. 6d.

This is the second edition of a little book which first appeared in 1933, and which has undergone very little alteration. Within the compass of its hundred pages the author succeeds in presenting the main facts regarding the evolution of one of the most ancient branches of medical science, a branch which was already well developed when the Ebers Papyrus was written, about 1550 B.C. The practice of ophthalmology must be founded upon anatomy, and it is interesting to note the changing views regarding the structure of the eye, as revealed in the six well-chosen illustrations in this work. It is also of interest to note that the invention of spectacles, usually attributed to Roger Bacon but probably of much more ancient lineage, did not at once meet with general acceptance, and for centuries "weak sight" was treated by the instillation of drops or "collyria." Astigmatism was not recognised until 1801, and the trial case of lenses made its first appearance in 1843. The writer's account of the progress of ophthalmology in the British Isles shows how fierce was the conflict with quackery in the early days, but it also demonstrates how admirable was the pioneer work of such men as Mackenzie, Bowman, Argyll Robertson, and others. There is a good index, and a short, but useful, bibliography.

## VAGINAL HYSTERECTOMY

By A. S. CAMPBELL, M.D., C.M., F.R.C.S. (Can.), F.A.C.S.

Associate Professor of Obstetrics and Gynaecology, McGill University,  
Montreal, Quebec

AS early as the fifth century, operations which might be interpreted as vaginal hysterectomies were performed at intervals. Those operations and a few which followed are, however, more of historical interest than of surgical importance.

In the latter part of the nineteenth century, vaginal hysterectomy received sporadic attention, but not until the past decade did it gain any degree of popularity. In some quarters the pendulum may have swung blindly towards this operation, in that it has come to be recommended for the treatment of a wide range of pelvic symptoms, regardless of their cause.

In the first place, vaginal hysterectomy should be undertaken only by those who are thoroughly familiar with pelvic lesions and all their ramifications, and who possess, in addition, a thorough working knowledge of the anatomy, topography and so-called dynamics of the female pelvis. Moreover, upon contemplating a vaginal hysterectomy, the surgeon should assess his own dexterity and take cognisance of his limitations; further he cannot afford to overlook the efficiency of his assistants and the circumstances under which he is operating.

Before proceeding with a vaginal hysterectomy, it is essential that other lesions within the pelvis (and it is unfortunate that pelvic lesions rarely exist singly), be excluded. If *unrecognised* pelvic inflammatory disease or endometriosis exists, or if these lesions are recognised but their extent minimised by the operator, the difficulties encountered may, from a technical standpoint, be unsurmountable. In short, one should satisfy oneself that the pelvic organs are mobile before attempting the operation. In large centres, some 30 per cent. of patients referred to the gynaecological clinic have had previously some form of lower abdomen operation, in which case, the adnexa, if not the uterus, are frequently involved in dense adhesions. Whether the peritoneal cavity be opened through a vaginal or an abdominal approach, it is imperative that at the conclusion of the operation the peritoneum be left intact. It is quite apparent that where there is much destruction of peritoneum from adhesions, inflammation or other causes, reperitonealisation by the vaginal route will be difficult, unsatisfactory, and even impossible.

Paper presented to the Edinburgh Obstetrical Society on 9th June 1948.

While at first glance it would seem superfluous and indeed absurd to explore the uterus prior to vaginal hysterectomy, it is nevertheless the first step in the operation. The finding of tissue on curettage which (on gross inspection) is suggestive of malignancy, obviously should alter one's plan of attack. In order to prevent embarrassment it is considered wise that the surgeon prepare his patient psychologically for such an eventuality. If carcinoma is found in the fundus, the lesion should first be treated according to the currently accepted formulæ. Whether or not repair of the damaged birth canal be undertaken simultaneously with the introduction of radium is a matter of personal preference, but it is only reasonable that since the damage has existed for years, temporary postponement of repair should not be considered important. In most clinics, following radiation for the treatment of carcinoma of the fundus, it is recommended that the pelvic organs be entirely removed by the abdominal route, at which time the damaged birth canal may be conveniently repaired.

If a uterine tumour fills the pelvis, or for that matter is as large or larger than the foetal head, it is apparent that apart from the mechanical difficulties involved in delivering such a uterus, one may unexpectedly encounter an associated lesion. Morcellation to facilitate the delivery of a large tumour, as practised by certain operators, is not a sound surgical procedure.

Moreover, in dealing vaginally with relatively large benign tumours, in addition to the mechanical difficulties encountered, there is to be considered the increased operating time, the amount of tissue traumatised, the blood loss, the shock, the ever-present danger of overlooking an associated lesion and the more than probable possibility of completely deperitonealising the pelvic basin. Any one of these, or a combination of several, may seriously jeopardise the patient's life or her subsequent well-being. It should therefore be *axiomatic* that no attempt be made to remove per vaginam a uterus which is larger than an eight weeks' pregnancy, a fixed uterus, or one with associated pathological lesions palpable in the pelvis or fixed adnexa. Only one with very broad experience should make exceptions to this rule.

Notwithstanding such manifest disadvantages and limitations as the aforementioned, there yet remains a very considerable proportion of gynaecological patients, in the surgical treatment of whose disability vaginal hysterectomy would seem to be the operation of choice. The following are the more common conditions for which vaginal hysterectomy may be considered :—

1. Prolapsed uterus.
2. As part of the technique for repair of enterocele.
3. Lesions of the cervix other than those proven to be carcinomatous.
4. Lesions of the uterus other than malignancy or those mentioned in the previous paragraphs.

In the selection of an operation for the reduction and cure of a sacropubic hernia, the factors possibly predisposing to such a condition should be borne in mind. It is therefore not inappropriate at this point to remind oneself of the common causes of procidentia, *i.e.* :—

1. Secondary :—

- (a) over stretching of the so-called pelvic ligaments (birth trauma),
- (b) Congenital enterocele.

2. Weakness in the musculature :—

- (a) inherent,
- (b) subsequent to prolonged systemic infection,
- (c) from debilitating diseases such as :—
  - (i) diabetes,
  - (ii) pernicious anæmia.

3. Congenital defects in recto-vaginal septum.

4. Disturbed innervation, *e.g.* spinal cord lesion from pernicious anæmia, lues, etc.

With the isthmus of the uterus at normal level, the practice of amputating a greatly hypertrophied or deeply lacerated cervix coincidentally with the repair of the birth canal is indisputably sound. Manifestly, however, one must be confident that such a cervix and that portion of the uterus above the internal os are free from malignancy.

The current practice, however, of amputating the cervix and involuting the mucous membrane as part of the repair, in many instances leaves much to be desired. Experience has demonstrated that too frequently the inverted mucous membrane does not "take" over the entire crater. Small pouches are consequently formed, which becoming filled with mucus, blood and debris, are in effect veritable cesspools. The symptoms then are those of an intermittent mal-odorous vaginal discharge and from the cellulitis (fortunately of low grade) the patient constantly complains of a burning or throbbing in the pelvis, as well as a general lack of well-being. As an alternative to such a procedure the cervix can be amputated with the actual cautery.

After protecting the vagina with retractors the cervix is drawn down firmly when amputation is gradually effected by encircling the cervix with the actual cautery kept at low temperature. The resulting amputation is crater like and within some three to four weeks following the separation of the slough the area becomes completely epithelialized.

It cannot be denied that there is a very considerable merit in those operations primarily designed for the cure of procidentia which include amputation of the cervix, but if the cul-de-sac is not occluded and the

utero-sacral ligaments not utilised to the fullest advantage, too frequently the patient does not experience complete relief from her symptoms. Further it is well to bear in mind that when the individual is past the child-bearing period that portion of the uterus above the internal os, in addition to being relatively inert, in too many instances serves no other purpose than that of a potential menace.

Patients with the debilitating deformity of procidentia must, in the first instance, be carefully assessed and any surgical plan of attack weighed with mature judgment. Various types of operation have been devised but unfortunately the results have been frequently disappointing. With vaginal hysterectomy, as with any other undertaking aiming at reconstruction, one's goal should be primarily one that will ensure the well-being of the patient.

In a patient in the fourth decade with a living family, who has such a degree of birth trauma that the cervix protrudes into or through the vaginal orifice, the type of operation best suited is a controversial point. Most authorities are at present leaning towards the opinion that repair of the vagina, under such circumstances, might well include vaginal hysterectomy.

While, therefore, the removal of the uterus is elective, there is still a large group for which vaginal hysterectomy is particularly designed. In those mothers in the fourth decade, who, in addition to suffering from damage to the birth canal, present a cystic, deeply-lacerated, everted granular cervix from which, in many instances, a polyp protrudes, the uterus should be regarded as a potential menace rather than as of future use. In the interest of the patient's health, it is therefore much wiser to remove the uterus than to amputate the cervix and blindly disregard the wisdom of extirpation.

Fortunately an enterocele of distressing proportion is infrequently encountered in the child-bearing period in those whose pelvic anatomy is otherwise normal. On the other hand in those past the menopause, coincident with general muscular regressive changes, even in the absence of any marked degree of descensus uteri, a symptomless enterocele can frequently be demonstrated. Further in over 90 per cent. of cases with procidentia, there is an associated enterocele of varying degrees.

An enterocele due primarily to a congenital defect in the recto-vaginal septum, or one which is secondary to procidentia, is in effect a hernia. In its repair, therefore, the surgical principles involved in herniotomy must be observed. Simple repair of an enterocele, while giving satisfactory anatomical results, does not altogether ensure the subsequent comfort of the patient.

By removal of the uterus incidental to the surgical repair of an enterocele, the structures necessary for such repair are made definitely more accessible. Further the symptoms of pressure on the rectum of a scarred tissue mass which too frequently follow the simpler repair of this type of hernia are thus obviated. A very considerable experience

has made it quite apparent that the incidence of recurrence of such a hernia, and the subsequent comfort of the patient following vaginal hysterectomy with obliteration of the hernial sac, justifies the procedure.

Often in addition to a damaged birth canal, there is a history of irregular uterine bleeding, the investigation of which may reveal a uterine polypus or polypi, hyperplasia of the endometrium, or small submucosal leiomyomata. Here it would seem that the removal of the uterus vaginally at the time of repair is preferable to the alternate double procedure of repair of the birth canal and abdominal hysterectomy, or the less advisable combination of intra-uterine radium and repair.

In the absence of any detectable lesion in the urinary tract, the symptom of so-called stress incontinence is probably too frequently attributed to damage to the support of the pelvic urinary apparatus. An extreme degree of birth trauma may be present without such a symptom, indeed it is worthy of note that stress incontinence relatively rarely accompanies procidentia. On the other hand it is not infrequently encountered in the absence of any defect in the supporting mechanism of the pelvic viscera, and in such circumstances one must look further afield for an explanation.

Following an intra-abdominal operation (particularly a sub-total hysterectomy) the bowel on occasions becomes adherent in the vicinity of the bladder when urinary incontinence, similar to that experienced in diverticulitis, is not infrequently observed. Obviously under such circumstances the pathological arrangement of the abdominal viscera are responsible for the symptom of stress incontinence, rather than a defect in the urethral or bladder supports.

By a somewhat similar mechanism an extremely pendulous abdomen may embarrass the control of the bladder. When arranged under a tightly fitting supporting garment, the fatty tumour is capable of pressing on the bladder. Under such circumstances the deformity of the anterior abdominal wall should receive attention, either by discontinuing the practice of dress or by surgical removal of such an overhanging lipoma.

The foregoing are but examples of the many conditions, the mechanics of which irrespective of the degree of birth trauma, may give rise to distressing urinary symptoms.

**PREPARATION.**—Both local and systemic factors must be considered in the patient's preparation. Just as a great deal of the success of any operation depends upon operating on relatively healthy tissue in as clear a field as can be prepared, so the safety of the procedure depends upon a careful pre-operative regimen directed towards improving the patient's general health. To quote Lord Moynihan: "We have made surgery safe for the patient, we must now make the patient safe for surgery."

All patients over fifty years of age, together with those under fifty years of age giving any history of cardio-vascular symptoms, should have an electro-cardiogram pre-operatively, if for no other reason than for the purpose of record.

The sugar tolerance curve should be established for it has been found that a sizable number of those patients with damage of the vaginal supports have a reduced sugar tolerance. When such is the case, healing is retarded and complications increased, unless this reduced tolerance is combated pre-operatively.

Similarly by a pre-operative knowledge of prothrombin time the incidence of thrombo-phlebitis may be reduced. The timely administration of heparin and dicoumarol post-operatively, as indicated by prothrombin time, should go far to avert the calamitous embolism.

Patients showing more than eight white blood cells per high power field in a catheter specimen of urine should receive appropriate amounts of sulfonamides pre-operatively in the hope that the causative organisms are sulfonamide sensitive. As previously mentioned the underlying cause of urinary symptoms may be remote. A cord lesion giving rise to symptoms of the urinary tract may be the initial manifestation of pernicious anæmia and not infrequently preceding the characteristic blood picture of the disease. As the ureters are so frequently embarrassed in procidentia, in addition to blood urea estimations, it is considered prudent to visualise directly or indirectly the entire urinary tract.

Upon completion of the clinical and laboratory investigation, the patient should be given three or four days "pre-operative convalescence." During this time, fluids, fruit juices and milk are liberally given, rest is induced by sedation, and debilitated patients are given intravenous proteins for at least twenty-four hours prior to operation.

The preparation of the operative field also demands attention. As senile vaginitis is most inimical to primary healing either from tissue changes or infection, an œstrogen preparation should be given by mouth in moderate dosage. Excessive œstrogen therapy will, however, produce a very friable and hyperæmic mucosa which may present considerable difficulty in suturing. If this effect is produced, as judged by its hyperæmic appearance, the operation should be delayed until the mucosa has returned to a more normal state.

During the pre-operative period, lactic acid douches, one drachm to the pint, seem to improve the state of the operative field and reduce the number of pathogens present. If the mucosa is thick and of the consistency of pachydermia, or there are decubitus ulcers, the prolapse should be reduced and supported by tampons; these are removed daily and reintroduced after douching.

While in most centres the operation of total hysterectomy has wisely replaced that of sub-total, or incomplete hysterectomy, the neglected cervical stump is still common. This may fall heir to all the diseases

of the cervix in the intact uterus. The vaginal operation for removal of a non-malignant unhealthy stump is essentially the same as that for removal of the entire organ.

It not infrequently happens that inversion of the vagina occurs subsequent to incomplete, complete, or vaginal hysterectomy. Here, apart from actually removing the uterus, repair of such a hernia is satisfactorily accomplished by adopting the same technique as that employed in repair of an enterocele associated with procidentia.

There are three accepted methods for removal of the uterus vaginally. The principles involved in these are :—

1. The base of the broad ligament (so-called cardinal ligaments) are employed to support the pelvic basin.
2. In the clamp method (Kennedy and Price), the cicatrix, following the removal of the clamps, forms a dense keystone of scar tissue, which prevents subsequent prolapse.
3. The utero-sacral ligaments are so sutured into the pubo-cervical fascia as to form a continuous fascial plain extending from the pubis to the sacrum.

The main features in the technique of the latter are :—

1. That the hernial sac should be shortened and securely closed.
2. That all ligated vessels be exteriorised.
3. That the utero-sacral ligaments be isolated and fixed into the pubo-cervical fascia.

**TECHNIQUE.**—After preparation of the field of operation, the cervix is firmly grasped with a *double-toothed teneculum* and drawn downward. An Allis forceps may be attached to the mucosa immediately posterior to the urethral orifice. With a sharp knife a racquet-shaped incision is made in the mucosa, extending from the urethra and surrounding the cervix. To minimise hæmorrhage the opening thus outlined should be only of sufficient size to permit the delivery of the uterus.

Having incised the mucous membrane, the cervix is drawn forward and upward. The mucous membrane in the posterior fornix is now pushed upward for a distance of approximately one inch so that the base of the broad ligament becomes clearly visible, the utero-sacral ligaments standing in relief.

The racquet-shaped flap of the mucous membrane of the anterior vaginal well is freed at its upper end and grasped with a gland forceps. Usually by gentle downward traction the mucous membrane may be readily separated from the base of the bladder. Occasionally, however, it is necessary to employ dissection to obtain the proper line of cleavage between the mucosa and the cellular tissue supporting the base of the bladder. If one encounters scar in this area (particularly the type



following previous operation), the dissection should be most cautiously performed and a great deal of care exercised, so that the bladder wall which not infrequently is involved in such scar may not be torn. All bleeding points should be ligated.

The forceps attached to the flap of the anterior vaginal wall along with the tenaculum to the cervix are firmly held in the left hand. With a small abdominal sponge over the thumb of the right hand, the base of the bladder can be readily pushed upward. If it is not readily freed, the adhesions may be snipped with the scissors, after which the bladder can be pushed well up on the anterior wall of the uterus. Great care should be taken in this step of dissection, as not infrequently a small diverticulum of the bladder is present which may easily be cut or torn across.

The cervix is now drawn well forward by an assistant. With dissecting forceps held in the left hand the submucosal tissue in the posterior fornix is firmly grasped and incised with scissors. The lower end of the cul-de-sac is now opened. Occasionally the cul-de-sac is not readily accessible, as the reflection of the peritoneum of the posterior wall of the uterus may be at a relatively high level. When the cul-de-sac is opened, the scissors are inserted and opened to enlarge the opening, as in Hilton's method.

A small abdominal sponge with a tape attached is then inserted into the cul-de-sac. The sponge, having been first immersed in an aqueous solution of acriflavine, is wrung out before insertion. The function of the sponge is twofold :—

1. It prevents soiling of the pouch of Douglas ; it absorbs blood which may enter the cul-de-sac.
2. It prevents the bowel or omentum from gravitating into the field of operation.

With the cervix drawn downward and to the left, the index finger of the left hand is inserted through the opening in the cul-de-sac and passed along the posterior aspect of the utero-sacral ligament. The utero-sacral ligament can be readily identified when put on the stretch. At this point, so as not to grasp the ureter with the clamp, the cellular tissue in the region of the uterine artery should be further pushed upward.

Having applied a Wertheim clamp to the utero-sacral ligaments on each side and cut between them and the cervix, more of the broad ligament is put on the stretch with the index finger of the left hand in order to bring each uterine artery into view ; these as well as the broad ligaments on each side are clamped by one or two Wertheim clamps and divided from the uterus.

To deliver the fundus of the uterus, the index finger of the left hand is passed behind the uterus, putting the uterovesical fold of the peritoneum on the stretch. This fold is then incised, and the fundus

of the uterus is delivered through the incision and grasped with a "bulldog tenaculum." The left round ligament, utero-ovarian ligament and fallopian tube now brought into view, are clamped with Mayo-Kocher clamps and divided from the uterus. (It has been found that these clamps, being relatively straight, are more suitable for clamping the upper portion of the broad ligament than the Wertheim clamp.)

The uterus is now carried to the left, the right broad ligament is put on the stretch, secured with two or three similar clamps, and divided, thus freeing the uterus completely.

Following the removal of the uterus all bleeding points are ligated separately and clamps removed. The sutures affixed to the utero-sacral ligaments are held and not cut.

By grasping the peritoneum with Allis forceps, the cul-de-sac can be adequately exposed. A purse-string suture is then inserted into the peritoneum, care being taken not to injure or incorporate the ureter by taking a deep bite with the needle.

The purse string suture should be inserted as high in the cul-de-sac as possible and tightened as the taped gauze in the cul-de-sac is gradually being withdrawn. The peritoneal cavity is now completely occluded while the end of all severed vessels lie extraperitoneally. The free ends of this purse string suture are held, to be later employed.

At this point the redundant portion of the peritoneum may be resected.

The abdominal cavity having been occluded, the mucous membrane of the anterior vaginal wall is then grasped and held with a series of Allis forceps or lung clamps. With gauze over the index finger, the mucosa is further separated from the underlying tissue.

Since the blood supply becomes more abundant as one approaches the pubic arch, by thus delaying the complete separation of the mucosa, embarrassing bleeding is obviated. This step in the technique ensures a relatively dry field until after the uterus is removed and the peritoneal cavity closed.

On a fistula needle the sutures previously ligated to the utero-sacral ligaments are fixed into the pubocervical fascia at its junction with the anterior portion of the urogenital diaphragm. By this arrangement the bladder is properly supported on a platform formed by the pubocervical fascia and utero-sacral ligaments.

The purse-string ligature occluding the cul-de-sac is brought around the lateral sides of the utero-sacral ligaments and tied. By so doing, the potential dead space between the peritoneum and the new pelvic floor is obliterated. At the same time, the two utero-sacral ligaments are firmly brought together. These ligaments may be further drawn together by two or three interrupted sutures. To prevent a hernia in the vault, it is important that there should not be a large hiatus anterior to the rectum.

The redundant mucosa of the anterior vaginal wall is now put on the stretch and resected with the scissors. Sufficient tissue should be left to ensure against tension on the closing sutures.

Closure is made in the anterior vaginal wall by four or five interrupted sutures in the pubo-cervical fascia. Some eight or nine sutures of No. 00 plain catgut are employed in approximating the mucosa.

In the repair of the posterior vaginal wall, the vagina is grasped with an Allis forceps on either side at the junction of the scar with the mucous membrane. A third Allis forceps grasps the skin immediately anterior to the anal ring. The incision, it will be noted, is not transverse but rather V-shaped. Such an incision prevents a redundancy of the perineum. The edge of the mucosa flap to be removed is grasped with gland forceps and elevated. The rectum is gently separated from the mucosa of the posterior wall by gauze dissection. Rarely is sharp dissection required for this step in the operation.

The mucosa of the posterior vaginal wall having been freed from the rectum to the upper limits of the apparent rectocele, a V-shaped portion is outlined and two crushing clamps applied. With a sharp knife the mucosa is resected along the lateral side of the clamps. By this method of resecting the mucosa of the posterior wall, the flap is accurately and regularly mapped out, and the edges are cut. When a scissors is used, the edges are more or less crushed and union is not so satisfactory.

The perirectal cellular tissue is then approximated with a series of interrupted catgut sutures, while the separated levator ani is drawn together by three interrupted sutures.

In order to retain the normal topography of the perineum, it is essential that the sphincter vaginæ be attached to the sphincter ani externus, by a subcutaneous suture. Otherwise, the sphincter vaginæ will eventually draw the skin of the perineum forward, partially barring the vaginal orifice, while the sphincter ani, if not firmly fixed to the sphincter vaginæ anteriorly, will tend to be drawn backward, causing a distressing deformity of the perineum—the so-called "sacral anus."

At the conclusion of the operation, the vagina is packed with emulsion gauze and an indwelling catheter inserted into the bladder.

The packing is removed at the end of a twenty-four-hour period, while the catheter is not disturbed (other than releasing the clamp every four hours), until the fourth day.

COMPLICATIONS.—If the patient is thoroughly investigated pre-operatively the complications following vaginal hysterectomy should be neither frequent nor serious.

There are, however, certain post-operative complications peculiar to vaginal hysterectomy. These may be attributed to many factors.

In the first instance, the bladder in procidentia ordinarily is not enlarged from urethral obstruction, but rather from atony. The tone

in such a bladder can be re-established by the use of an indwelling catheter or, in refractory cases, a so-called tidal drain.

One, too, must not lose sight of the fact that as a result of the operation, the innervation of the bladder has been insulted either from laceration of the nerve supply at the time of operation, or from subsequent œdema.

The catheter ordinarily is removed on the third post-operative day. Thereafter, the patient should be catheterised every six hours immediately following voiding. If after the sixth day, the patient is unable to void and there is still a considerable residual urine,  $1\frac{1}{4}$  fluid ounces of "mercurochrome" instilled into the bladder has been found to be particularly effective in encouraging voiding. When the residuum after voiding has diminished to approximately 30 c.c., it may be considered that the bladder needs no further attention.

Abscess of the vaginal vault is fairly common, but again frequently avoidable. It occurs most often in patients with senile vaginitis and in those who have not received pre-operative attention.

Persistent leucorrhœa in the absence of granulation in the vaginal vault is suggestive of a peritoneal fistula. If at the time of the operation the distal end of the fallopian tube, or a fragment of omentum is caught in the purse-string occluding the cul-de-sac, such a fistula may result.

The vagina is shortened only in those cases where at the time of operation the recto-vaginal septum has been found wanting.

Atresia of the vagina is to some extent avoidable. It occurs most commonly in those in whom menopausal symptoms have not subsided; at this point, contractures are very more apt to occur than in those in a younger or older age group.

In a relatively large series of vaginal hysterectomies performed, incidental to the surgical relief of procidentia, subsequent herniation of the vaginal vault occurred in less than one per cent. These, no doubt, resulted from failure adequately to occlude the hiatus bounded anteriorly by the junction of the two utero-sacral ligaments and posteriorly by the rectum.

In a certain proportion in the advanced age group, reduction of the hernia and re-establishment of bladder and rectal support should be the primary object of the operation, while reconstruction of the vaginal canal is of secondary importance.

We, therefore, must appraise our results not only on the permanency of reconstruction, but also on the subsequent well-being of the patient.

In gynecological surgery, and more particularly in vaginal surgery, one is more and more forced to appreciate the interdependence of the various branches of medical science. A fair understanding of these is necessary in order to obviate the failures which too frequently follow vaginal surgery.

Briefly, one's views on vaginal hysterectomy are that if in the absence of a damaged birth canal, extirpation of the uterus is indicated,

its removal per vaginam is not a simple procedure and, in general, should not be considered. On the other hand, if there is any marked degree of procidentia, providing there is no lesion in the pelvis and the uterus is not unduly large, a most satisfactory result can be obtained by the combined operation of vaginal hysterectomy and vaginal reconstruction. The prolonged cul-de-sac which accompanies the displacement, can be occluded and those structures necessary in the reconstruction of the pelvic basin and the vaginal canal made more accessible.

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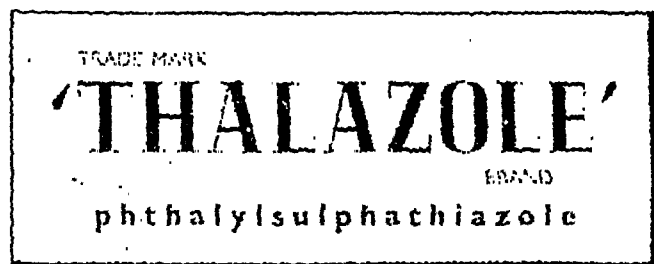
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# Edinburgh Medical Journal

July 1949

## MEDICAL RESEARCH AS AN AIM IN LIFE

By SIR HENRY H. DALE

MR PRESIDENT.—I am proud of the honour you have done me in inviting me to address your Royal Medical Society with its long record and ancient traditions. Of two other Chartered Royal Societies with which I have had some connexion, the Royal Society of London for the Advancement of Natural Knowledge to give it its full title, which by right of seniority has come to be known as *the* Royal Society, antedated your Society in foundation by some 76 years; on the other hand the Royal Society of Medicine, centred also in London, even if we date it from the foundation of its principal constituent, the Royal Medico-Chirurgical Society, has to admit to being your junior by about sixty years. I like the ripeness and dignity of old traditions; we may sometimes need them in these days as a check on haste and exuberance; but we all know their detrimental possibilities, if they are just blindly worshipped, without any serious attempt to blend and harmonise them with healthy and necessary modern development. When, therefore, I was invited to address your ancient Society, I thought it might be appropriate for me to speak to you about something which, as a consciously-recognised development of medical activities, is a comparative novelty—medical research, which happens to be also the only kind of medical activity about which I am entitled to speak from first-hand knowledge.

The half-century of which the end is now not far ahead of us has seen a great widening of the range of careers open to one who is newly graduated or qualified in medicine. His choice among these may seem to present a peculiar difficulty at the present time, when the framework of medical practice, and especially of general, family practice, has been subjected to so sudden and so drastic a strain of reconstruction, of which the ultimate effects cannot as yet be predicted with any confidence. I suspect that some of those who, till the last few years, might have regarded general practice as their obvious aim, providing them with the kind of opportunity for which they felt themselves to be naturally fitted, in the social setting most congenial to their tastes and aptitudes, may now be giving a closer consideration to alternative careers, such as preventive medicine, public health administration, or one of the various lines of academic or professional

A Lecture delivered to the Royal Medical Society, Edinburgh, 21st January 1949



activity in which a medical man can now earn a modest remuneration, while using his special training for the benefit of the community. And among such other possibilities will be a life in which medical research provides a major interest, even if it does not constitute the main claim to a livelihood.

Recent years, indeed, have seen a remarkable development of the general interest in medical research as an activity to be encouraged, and a rapid extension in more than one direction, of its recognised scope. On the one side there has been a noteworthy growth, or perhaps one should rather say a conspicuous revival, of our perception of the extent to which the direct study of disease in man can partake of the nature of a genuine scientific research, to the great benefit of the advance of medical knowledge. My late distinguished friend Sir Thomas Lewis devoted much of the energies of his later years to a veritable mission, in which he urged two different aspects of this development upon our notice. On the one hand, he insisted with a burning conviction that research in clinical medicine must be regarded as a distinct and independent branch of experimental science, having its own methods and its own special technical equipment, as clearly separate from those of the laboratory disciplines of physiology, pharmacology and pathology, with their appeal by analogy to experiments on the lower animals, as these were from the methods special to other departments of science. It seems to me likely that Lewis was basing that claim largely on experience of his own brilliant success in the use of the experimental method for the analysis of symptoms which disease had produced. He seemed to me to underestimate the impediments to its use, on man himself, for the study of other and very important aspects of a disease, such as its ætiology, involving deliberate attempts to produce it, and therapeutics, involving the trial of new treatments. There is a clear case, I think, for getting all the accessible information on such matters from experiments on the lower animals, in the laboratories of pathology and chemotherapy, before seeking a final extension of some of this knowledge to the case of man, which may necessitate and justify experimental confirmation and trials on human patients, when the safety of the trials and the co-operation of the subjects are assured. Lewis was at least equally concerned to establish a tradition for clinical research as a whole-time career in itself, and to get rid of a convention which had long made it depend, for its opportunities, mostly on the mixed experience of a visiting and consulting physician, and for its financial support on his private practice. In this direction I think that Lewis was adding the impulse of his convincing advocacy and his inspiring leadership to a current of opinion which had already been gathering energy and volume for several decades on the European continent, and in the United States of America. Its vigorous flow in this country could hardly, I think, have been long delayed, in any case; but Lewis had every good reason for wishing to accelerate it.

When I said that medical research had been extending its recognised scope in more than one direction, I had in mind the obvious fact that, even before the beginning of this outburst of interest and this organisation of activity in directly clinical research on disease, there had been, on the other hand, a rapidly growing recognition of the extent to which progress in medical knowledge and its command of technical resources were becoming dependent on researches in a widening range of contributory sciences. Less than a century ago, even within the lifetime of some who are still living, the whole of the experimental background of medical science was still comprehended in the conception of "physiology," which had then, of course, not become clearly separated from anatomy. To-day, if you survey the whole range of the natural sciences—chemistry, physics, even some chapters in the applications of mathematics, and the group embracing all the different fields of functional and systematic biology, apart from those normally figuring in a medical curriculum, you will find it practically impossible to trace any clear or continuous boundary of demarcation, between what is already of obvious significance to the progress of essentially medical knowledge, and what appears still to lie beyond the possibility of such a connexion. It would be difficult indeed, as yet, to predict any medical interest for the investigation by astronomers of the extragalactic nebulae, or for the exploration of the higher reaches of pure mathematics by those whose minds can operate in that intellectual stratosphere. He would be a rash speculator, however, who would to-day exclude anything, in the whole range of natural knowledge, from the ultimate possibility of some medical application. Nobody, for example, is likely to have thought, but a few years ago, of the bending of the path of an electron in a magnetic field, or the disintegration of the atom of a heavy element under neutron bombardment into radio-active isotopes of other elements, as phenomena likely to have a special importance for the advancement of medical knowledge by research.

Yet, when the physical problems concerned with the design of the electron-microscope had been solved, and new orders of critical resolution and effective magnification had thus been brought within reach, it was soon evident that a large part of the interest in this new physical weapon was becoming centred upon its applications to problems of essentially medical significance, such as the nature of ultra-microscopic infective agents, viruses and bacteriophages, or the dimensions and shape of bacterial flagella. And when the advance of nuclear physics in another direction had taken a leap forward during the war, in this case behind a thick curtain of military secrecy, and the artificially contrived liberation of atomic energy by nuclear fission had thus become an accomplished fact, apart from further concern with destructive possibilities, and perhaps by an instinctive recoil from them, attention seems to have become first centred on the use of the full range of new radio-active isotopes, which had incidentally

become accessible, for medical researches into problems of metabolism and for new methods of therapeutic radiation. We might even suppose that the conscience of the human race, or of those sections of it which can fairly be credited with so uncomfortable an attribute, had found an offset to the horrors of Hiroshima and Nagasaki, in even a speculative prospect of doing something for neoplastic diseases, in particular.

Only a few decades ago organic chemistry, having been led far from its original objective into explorations of the limitless possibilities of artificial synthesis, had come to look with disparagement on the efforts of the newly self-conscious biochemistry. Biochemistry had come into being to deal with the formidably complicated chemistry of life and its products, which organic chemistry had, for a time, almost deserted. "Tierchemie ist Schmierchemie," was a catchword of those days; animal chemistry, they thought, dealt with smeary, indefinite messes, and was too repulsively difficult for a real chemist to expose himself and his reputation to the risks of contamination from its contact. To-day the pendulum of opinion has swung far back indeed, and we now find some of the world's leaders in organic chemistry eagerly grasping the opportunities offered by the chemical problems of life and its products. It was not merely, then, the emergency of war which so readily induced the leading organic chemists of the English-speaking world to combine in a study of the structural constitution of Fleming's penicillin, when Florey, Chain and their colleagues had demonstrated its transcendent medical interest and its chemical accessibility. You have heard, no doubt, that this study soon revealed the existence of several penicillins, differing from one another in minor points of constitution, and even led to the confirmation of this latter, in one case, by synthesis. Before that stage was reached, however, it had been necessary further to invoke the aid of a specialised physical technique, X-ray crystallographic analysis, as a guide to the final choice between alternative structures, which the chemical data would fit equally well. And, to complete that side of the picture, we should note that the interpretation of the spot-pattern of the X-ray spectrograms, to reveal the spatial arrangement of the atoms in the molecule, would involve the application of a method of mathematical analysis discovered by Fourier in 1822. This was regarded then, and for long afterwards, as an intellectual achievement having an austere beauty of its own, as a kind of mathematical poem, but as remotely unlikely ever to find any sort of practical application. In physics as well as in chemistry, indeed, we can observe an eagerness to-day in many who are working at points of rapid progress, to apply their knowledge and technique to biological problems and thus to make contact with matters of more direct concern to medicine. Many other examples spring to mind, far too numerous for mention; but I must not leave an impression that physics and chemistry are alone important, among the extramedical sciences, for the advancement of medical knowledge. Let me, therefore, mention only one

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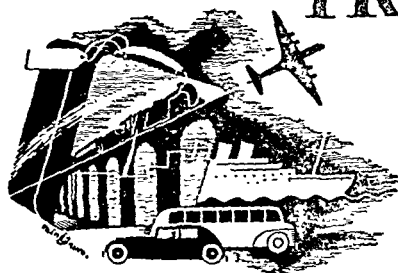
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other example, illustrating the unexpected medical value of what had seemed an almost freakishly specialised hobby in systematic zoology. A contemporary of mine at Cambridge, the Hon. N. Charles Rothschild, father of the present Lord Rothschild, had come up from school with the reputation of having been for years addicted to the collection and differential description of all the different species of fleas which could be found, in the fur or feathers of every kind of mammal or bird which he could contrive to examine. As you may imagine, we, his fellow-students, were disposed to regard this hobby as rather less practically useful than that of collecting stamps, and as lacking even the stimulus, which the latter would afford, of competition with rival collectors. And then, many years later, the Commission sent to investigate the Bubonic Plague in India came to the conclusion that a flea was the probable vector of the plague bacillus to man, and a rat the probable reservoir. It thus became urgently necessary to know the distinguishing characters of all the fleas infesting the animals with which human communities were in habitual contact; and the knowledge, to obtain which months or years of research might have been needed, was then found to be all ready to hand, and waiting to be used, in Mr Rothschild's collection and records.

I hope that, by citing these examples, I am not giving you the impression that I regard medical research as something so indefinite in its scope and so uncertain in its objective that it may be held to include practically any kind of research, in the whole range of the natural sciences. On the contrary, I think that the aim of medical research can be defined with unusual precision. Medical research is, surely, the investigation of the conditions of human health; of the causes and effects of its disturbance by disease or injury; and of the procedures conducive to its restoration. What I have been trying to make clear is that, apart from the direct approach to these problems by observation and experiment on the human subject himself, there is bound to be an ever-deepening extension of the quest for medical knowledge into territories with which other departments of science are primarily concerned. It is, further, of interest to recall how many of the independent sciences to-day—not only physiology and human anatomy, but botany, zoology and chemistry—took origin by budding or cleavage from the parent stock of medicine. The sciences as we know them now may remind us, indeed, of organisms which, when they have been multiplied and differentiated by many successive divisions and sub-divisions, find regeneration and renewal of vigour in conjugation.

There is a feeling abroad, indeed, in circles much wider even than those directly concerned with science, that medical research is an activity worthy of special encouragement. And a substantial expression of such encouragement has been forthcoming, from private generosity in many countries; in Britain in particular it has also been available, now for some thirty-five years, from an annual grant of

public money administered by the Medical Research Council. No man to-day who feels a genuine impulse to make medical research an aim in life, if he can give evidence of the requisite ability, training and character, ought to have serious difficulty, then, in finding the support required to enable him to put his aptitude for it to the test of a practical trial.

"Medical Research as an Aim in Life" is to be my subject, then, this evening; but before I say anything further about it, I ought, perhaps to make it clear that I am not concerned only with medical research as an exclusive occupation for the whole of a man's working career, or as the sole service to the community for which he expects to receive a livelihood. We should remember that nobody, until times which still seem recent to some of us, expected to be paid at all in this country for doing medical research; it seemed to be regarded as a form of mild indulgence, for the leisure of a man who earned his living otherwise, as by teaching, or practice—almost as a kind of addiction, to which he yielded if he could not help it. And, from one point of view, such a presumption might have a certain advantage, in making it at least likely that the few who did engage in medical research with any sort of persistence, were likely to have a natural gift for it, and an urgent desire to do it for its own sake. On the other hand, there was always the possibility that we and the world might be missing some mute, inglorious Harvey, or Lister, for lack of the opportunity to try the wings of his genius. I myself, through accident of opportunity, and contrary to all expectation, happen to have spent practically the whole of my working life in medical research. I have no feeling but gratitude for the exceptional privilege; but it has not led me to doubt that we shall always have to look, for the major contribution to the advancement of medical knowledge, to the men who are carrying a primary responsibility for teaching, or for the clinical care of patients. There is this radical difference, however, between the present position and that which persisted till thirty or forty years ago, that research, whether in the medical or other fields, is now recognised as a part of a man's service to the community, for which he may reasonably expect some remuneration; so that, if he is holding only a minor academic or clinical appointment, and has a large part of his time still free for research, he may expect by undertaking it to earn a significant supplement to his stipend. And the young man who has ideas which he is eager to exploit, or a problem at the solution of which he has a strong desire to try his hand, need not now feel that he is compromising his future, if he decides to test his powers as a research worker for a few years. Even if the result should not encourage him, or if circumstances should otherwise not allow him then to include research in a more permanent plan for his life's work, the time spent in gaining that experience will not have been lost. He will have had a direct and living contact with the methods of research, with its standards of evidence, its traps for the unwary

enthusiast, its excitements and its frustrations; and this first-hand experience of what research means will have given him, as nothing else could, a critical insight into the merits of claims made for new discoveries or advances, and will strengthen and vitalise all his work for the application of medical knowledge, whether in teaching, administration, or practice. In a real though limited sense, medical research may continue for him to be an aim in life, even though he may never again take a direct and active part in it.

On many grounds, therefore, and over a wide range of possibilities, as a whole-time or, more commonly, a part-time commitment, for an experimental period or for the whole of a working career, I do commend medical research, as an aim in life, to any of you whose natural instincts and aptitudes lead you in that direction. And, since research is the only activity in the field of medicine on which I can speak with any background of experience, I am going to ask your attention to some random reflexions on medical research—on the objects with which it has been undertaken, the methods by which it has been successfully pursued, and the ways in which an investigator may find and choose his problems.

(1) *What is the Object of Medical Research?* The answer might seem to be fairly straightforward; but it is tied up with a wider discussion of the purpose of scientific research in general, which is agitating some circles to-day. You have probably heard debate of the question, whether the true object of any kind of research is to discover scientific truth for its own sake, in complete aloofness from any immediate concern for its practical application, or, on the other hand, to discover means of improving the material conditions of human life. The effects of attitudes which appear so radically opposed, as thus stated, need not be so widely different in practice. For those who claim that the object of research should be to increase knowledge for its own beauty and excellence are usually ready, not only to admit, but even to claim, with the support of striking examples, that the widest and most important practical developments have, in fact, originated from the kind of independent and untrammelled pursuit of scientific truth which they advocate; while those who insist that the material enrichment of human life is the only true function of science—it is one of the doctrines of the so-called dialectical materialism, as most of you probably know—are willing, and even eager, to recognise the free advancement of even the most abstruse kinds of knowledge as a means to that material end, and therefore to honour and encourage it. There would not, on those lines, seem to be much difference, other than one of emphasis, between the practical effects of the two attitudes. And, for my own part, I regard it as a matter, of small concern, which of them a man may adopt as an ultimate theory or creed, provided that he do not attempt to give it too literal or rigid a practical application in the immediate problem of the planning or conduct of research. I have known a distinguished



colleague in medical research to be subject to tiresome inhibitions, because he had persuaded himself that there must be something unworthy or inferior about a research with any obviously practical objective. The danger is much more likely, however, to occur in the opposite direction. Benefit to human life, as an ultimate aim of medical research, is so obvious as to be almost a matter of definition; as a lure to benevolence, however, or as a guide to public policy in support of research, it has its too obvious dangers. A donor finds it difficult to refrain from specifying the problem on which his gift is to be used, and his choice is likely to be determined by sympathetic emotion; so that we may easily find, in some countries, funds subscribed for the attack on specified diseases in excess of those which can be usefully applied; and it must be obvious that the political credit which might accrue to one whose name was associated with the promotion of a successful attack on the problem, say, of rheumatism, must offer serious temptation to a Minister of the Crown.

We must be careful, then, not to confuse the theoretical or ultimate objective of research with the immediate policy of its planning. In medical research, as I said, the benefit of human health as the objective, is almost a matter of definition or nomenclature; I myself could not attach any other meaning to the word "medical." But in the immediate planning of his own activities by a worker in medical research, or in the planning which cannot but affect the allotment of funds available for its promotion, it is peculiarly necessary not to allow a sense of the ultimate objective to intrude in the guise of facile sentiment and popular appeal. We must beware lest it produce a tendency to favour long shots, short cuts, premature claims and even disreputable "stunts," and a corresponding tendency to discount and to disparage the patient and resolute pursuit of new knowledge, by a mind unclouded by any urgency for practical achievement and alert to follow any unexpected clue if it seems to promise a discovery of new significance, even in a direction remote from the lines of the original research. As a guide to policy which, in relation to our own researches, may not always be a matter of easy and confident decision, it maybe helpful to glance at the practice of some of those who have been responsible for some of the greatest advances in medical knowledge and, in due course, in medical practice.

William Harvey, it seems to me, approached his problems and used his opportunities of observation and experiment with just the instinct and habit of the inspired naturalist. "Nature herself," wrote Harvey, "is to be addressed; the paths she shows us are to be boldly trodden; for thus, and whilst we consult our proper senses . . . shall we penetrate at length into the heart of her mystery." And it was by such bold treading of the paths which nature showed him that Harvey was led to the first great medical discovery, by which he laid the foundation not only for a new physiology, but for all medical science. More than two centuries later Louis Pasteur, a mineralogist

and crystallographer, having discovered the mirror asymmetry of the crystals of the two tartaric acids and the preferential digestion of one of them by a mould, followed, with the alert vision of genius, the clue thus presented, and was led by it to further discoveries, which laid the first course in the foundation of the new science of bacteriology. Lister, it may be thought, took the clue, presented by Pasteur's work on the putrefaction of dead tissues, and applied it directly to the problem of suppuration in the living body. But Lister did not begin there; for many years he had been studying and describing, with the patient attention of a naturalist, the clotting of blood and the circulation through the capillary blood-vessels, and its changes with inflammation. Lister's experience as a free experimenter and observer, and the habit of mind which it had engendered, made him ready then to seize and to apply the analogy which Pasteur's work presented. And I have sometimes even thought that, if Lister could have withstood a little longer the irresistible appeal of human suffering, and could have given a few months to an independent, experimental study of the sources and the modes of access to wounds of the bacteria of suppuration, before he so directly applied his discoveries and assumptions, surgery might have been able to short-circuit the episode of the carbolic spray and, perhaps, to arrive much earlier at the modern routine of asepsis.

Paul Ehrlich's campaign of Chemotherapy has led, under his own guidance while he lived and later at the hands of those who have followed, to revolutionary changes in the prospect of sufferers from a whole range of diseases due to infections; and this might well be cited as an instance of a scheme of medical research producing just the kind of practical benefits for mankind at which it was deliberately aimed, by the man of genius who planned it. Even the re-examination of the therapeutic potentialities of penicillin, with the success which all the world knows, probably owed much of its stimulus to the earlier success of chemotherapy with artificial remedies. Banting and Best's discovery of insulin, again, could be cited as a striking example of medical research driving straight to the practical objective with which it was undertaken. In all these cases, however, we must not lose sight of the extent to which the ground had been prepared and the problem posed by antecedent researches, which had no such practical outcome in the relief of disease, but without which the experiments which eventually produced the remedial discoveries could not even have been devised.

Altogether, I think that we ought to retain a consciousness of the ultimate philanthropic purpose of medical research; but that our recognition of it ought to put us on our guard, lest we allow it to lure us into attempting short cuts, shelving exceptions, discounting difficulties, or making premature claims, in the hope that we may be able to reach some dramatically practical result, without submitting to the full and exacting discipline of science.

(2) And that leads me to say a few words more about the general

conditions under which medical research, like any other kind of genuine research, is carried out. It is so easy to get the impression, from the popular acclaim which greets its real or imagined achievements, that the life of the research worker must be passed at a level of emotional tension rather like that of a gambler. In past years I have had more than one young man come asking for an opportunity to do whole-time research, and to be paid for doing it, with little to show in the way of credentials, beyond a dislike for the idea of teaching or practice, and a feeling that research must, by comparison, be full of excitement and fun. I did my best to correct that impression. The research worker, if he is successful, may indeed have his moments of discovery and seemingly sudden revelation, from which he may experience more than a momentary exhilaration; but, in spite of what popular report may suggest, such moments do not come merely by fortunate accident. As has more than once been said, these sudden revelations, or seemingly accidental discoveries, come to the man who has earned them. More often than not they will have been earned by months or years of what may well have seemed an almost hopeless drudgery; by courage to face, without flinching or evasion, what T. H. Huxley called the tragedy of science—the shattering bereavement of seeing a beautiful hypothesis slain by an ugly fact; by an integrity which never shirks exacting standards of accuracy, or of critical control; and by humble acceptance of the answer which nature gives, when the questioner expected to get quite a different one and even tried, perhaps, unconsciously to extract it. Research may have its abundant rewards, but they are earned by submission to a stern discipline. And I think that it is a discipline from which a man would gain and keep something for a subsequent career in any kind of medical practice, administration, or teaching.

(3) Then, with regard to the finding and choice of subjects for research, let me say that I think that a not too exacting demand of duty in ward or clinical department, in laboratory, lecture-room or administrative district, bringing the holder regularly into living contact with the problems of health and disease, may even give him a definite advantage over one whose whole duty, for every day and all the time, is to do research and present its results. The difficulty, of course, is that duties and routine activities, which should provide a seed-bed of ideas and problems, and keep the worker's feet on the ground by preventing his attention from losing sight altogether of the ultimate significance of medical discoveries, are all too apt to become an embarrassing distraction, or a stifling incubus. How often a man must think that, if he could only get free from these insistent demands of daily obligation and be given the opportunity to concentrate his mind on research, he could push quickly ahead, towards the solution of an urgent problem which he has encountered. And, in many cases, there may well be substance in such regrets and aspirations. But there is another side to the picture. From my own experience, and

some knowledge of the experience of others who held appointment with me in a Research Institute, with no formal duty but to do research, to be fruitful in ideas and to multiply discoveries, I can testify that such a privilege brings with it its own psychological strains and difficulties. There is the teasing uncertainty, whether the condition or phenomenon, on which one has decided to centre his attention and his effort, has really such significance as one had supposed; the suspicion, when the research is not quickly fruitful in result, that one will be left with nothing to show for months or years of striving and worrying; and the haunting fear that the fountain of ideas, which seemed to flow so freshly, will dry up as youth and middle age give way to the years of decline, leaving him with no reserve of teaching or practice, by which he could have earned his bread and served his fellow men. I can testify that, under such conditions, many a man, who has eagerly embraced the freedom and seemingly unhampered opportunity of whole-time research, has looked with envy at the position of a colleague, who has no reason to fear that he is not justifying his existence and his stipend, if his research should hang fire for a time.

I have no reason to feel anything but gratitude for the opportunity which I have enjoyed; but the general position is very different to-day from that with which I began. There were then but scanty indications that medical research, in the intervening forty-five years or so, would so astonishingly and so radically change the whole aspect of preventive and curative medicine. There were no Beit Fellowships till some years later, and the Government's Medical Research Fund was still a decade or so ahead. So, when I was offered a research appointment supported by industry, I accepted, and held it for ten years; and I had no reason to regret the experience, from which I passed directly to the service of the Medical Research Council. And I am glad to think that there are men to-day who are doing work of high quality for medical science and finding problems in abundance ready to hand, in research departments supported by industry.

Looking at the possibilities now emerging, however, with the results of research at last making their full impact on practically every phase of medical activity, I think that, if I myself were starting again, I should probably be looking for the opportunity to do research in conjunction with some academic, clinical or laboratory appointment, in hospital or, perhaps, in public health service, and to find in one of these the problems for research. There is one particular kind of service to which, as it seems to me, the medical research talent of this country has not yet done its full duty, or made full use of its opportunity. I have in mind the medical service concerned with the health of our tropical colonies. The past record of British medical research activity in the tropics is one of which we have good reason to be proud; the names of Manson, Ross, Bruce, Leishman and others belong to a great history. Here, in any case, should be still an attractive prospect for the man with a pioneering instinct and a spirit of adventure, to work

in a field where many nuggets of new discovery are likely still to lie near to, or even on the surface, waiting for an alert vision trained in research to recognise them. And to-day, I expect that recruits with the right kind of ability, and some spirit of adventure, if that still exists, would find the training at their disposal on attractive terms, and would not have to fight for it, to find it or make it for themselves, as the old stalwarts did.

We need not go so far afield, however, or even into a whole-time service, to find opportunity presenting itself to the man with the true research instinct. James Mackenzie did the best of his epoch-making researches on heart disease and its treatment in time spared from a busy general practice in Lancashire. Dr William Norman Pickles, of Aysgarth, is to-day using the special opportunities of a general practice limited to the villages scattered along Wensleydale, for the scientific collection and analysis of data concerning the spread of epidemics of the common infectious fevers—data such as could not otherwise be obtained. If a man has the true impulse to do medical research, he will find the opportunity for it under conditions in which we have not yet learned to expect it.

We shall probably not all hold exactly the same opinion about the future of medical practice, and the effects on its value to the community of the new conditions which the National Health Act imposes. I think that we can all agree, however, that no pressure of form-filling, certificate-writing and report-making which a centralised administration may involve, must be allowed to weaken the personal, professional and scientific standards of the practitioner. Research has been providing, and will continue to provide, a new basis of scientific knowledge for increasingly certain diagnosis and for ever more directly effective treatment. Reorganisation of the basis of practice will have no value, unless it enables these results of research to be made more readily available to the patients whom they can help. We ought all of us, as a profession, to insist on the right to keep that flag flying, to let it be known that we have no use for changes which do not help us to regard medical research more clearly as an aim, to keep pace more easily with its progress, and to apply its discoveries more quickly and effectively, for the benefit of anybody who needs them.

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## THE OLD INFIRMARY OF DUNDEE, 1798-1855

By HENRY J. C. GIBSON, M.A., M.D.

Medical Superintendent, Dundee Royal Infirmary

ABOUT a hundred years ago there were two memorable days in the history of Dundee, whole holidays with all business in mill and factory, in shop and warehouse completely suspended, and with the roads and the new railways overtaxed with a vast concourse of country folk. All were crowding to see the processions and other celebrations which marked the visit of Her Majesty Queen Victoria in 1844; and they came in even greater numbers to observe the occasion when His Grace The Duke of Atholl, the Grand Master Mason of Scotland, laid the foundation stone of the new Infirmary on the 22nd July 1855. Tremendous enthusiasm attended the inauguration of this hospital for the sick and hurt, and from the outset it was assured of the confidence, affection and regard that had marked the history of its predecessor for over half a century.

### THE DUNDEE DISPENSARY

The foundation stone itself rests in a buttress immediately to the east of the central building, and in its hollow lies a glass vase with a multiplicity of contents, coins, stamps, papers, periodicals and almanacs and also documents relating to the first days of the venture, and among them a record from 1735 onwards of the Dundee Dispensary, the first voluntary agency devoted to the sick and hurt. This precious record, though placed in the centre of affairs, is unfortunately inaccessible; and so far it has not been possible to unearth any copy of the document or other account of the Charity prior to 1782.

In that year, however, the story begins to unfold itself. The Committee divided the town and parish into four districts, each served by a surgeon who visited the sick poor in their own homes and attended a few confinements with the assistance of a midwife, the day-to-day administration being assigned to an apothecary at a central shop. This local health service, with modifications to suit the needs of the day, continued its benevolent work under the Infirmary Board until 1911, when its activities, with the exception of the maternity district, were suspended on the operation of the National Health Insurance Act.

### THE PRÆSES AND FIRST CHAIRMAN

The revival of the Dispensary was, however, only the prelude to the foundation of the Infirmary, for some of its office-bearers at once

An address on the occasion of the inaugural meeting of the Scottish Society of the History of Medicine, 1948.



began to interest themselves in a wider scheme for in-door care. Among them, the Reverend Robert Small, D.D., the Minister of the Parish (Fig. 1) stands pre-eminent. Born at the Manse of Carmyllie, Angus, he belonged to a notable family, one of whom, a younger brother, William, filled the Chair of Mathematics and Natural Philosophy in the College of William and Mary in Virginia, and at whose table his friend Thomas Jefferson, the third President of the United States, "heard more rational and philosophical conversation than in all my life besides"; thereafter he returned to this country to be associated



*R. Small, Præses*

FIG. 1.—The Reverend ROBERT SMALL, D.D. (1732-1808). Præses and Chairman

with James Watt, the engineer. Dr Small himself is described as a man of sound understanding and an able exponent of the Gospel; and his papers include a notable homily, "On the Importance of the Poor illustrated." In 1791 he was chosen Moderator of the General Assembly of the Church of Scotland, though he had subsequently to appear before that Court in answer to a charge of failing to require his elders to subscribe to the Confession of Faith on their ordination. A classical scholar, Dr Small also attained distinction in natural philosophy, being a Fellow of The Royal Society of Edinburgh and the author of a considerable volume, *An Account of the Astronomical Discoveries of Kepler, including an Historical Review of the Systems which had successively prevailed before his Time* (1804). This learned, versatile and tolerant divine was tireless in his efforts to establish

the Infirmary on a sure foundation, guiding the preliminary meetings as Præses from 1793 onwards and being appointed the first Chairman, when the house was opened in 1798.

SIR ALEXANDER DOUGLAS, BART., M.D., F.R.C.P.ED.

Sir Alexander Douglas, Bart. of Glenbervie, one of the original physicians, was also intimately associated with these endeavours. Descended from the noble house of Angus and among them from Archibald Douglas, the famous "Bell the Cat," he studied at Edinburgh and at Leyden in Holland—the most celebrated schools of the day—as well as at London, and attained a position of eminence as Physician to the King's Forces in Scotland. The University of St Andrews admitted him to the Doctorate of Medicine in 1760 and the Royal College of Physicians of Edinburgh to their Fellowship in 1796. At the Infirmary he is chiefly remembered for his enthusiasm for electrical treatment, his concern to open a branch of the Dispensary in the West End of the town "for such patients as it is out of their power to attend the Apothecary's shop at the Infirmary," as well as for the influence he exerted among the landed gentry in the interests of the infant institution. "He was candid, upright and benevolent. The whole tenor of his life bore testimony to the kind affections of his heart, which were conspicuous not only in the humane and tender discharge of his professional duties for over fifty years, but in many acts of most disinterested liberality and beneficence." The Nova Scotia baronetcy, created in 1625, became extinct on his death in 1812.

Mr Robert Stewart also gave unstinted support, a surgeon distinguished in his profession, a man of culture and widely interested in literary pursuits. He had graduated Doctor of Medicine in Edinburgh in 1771, with a thesis on arthritic disorders.

THE FOUNDATION OF THE INFIRMARY

The first formal meeting of the subscribers, with Dr Small in the Chair, was held on the 16th March 1793, when it chose a representative committee of country lairds, the medical profession, members of the Town Council and the Nine Trades, together with merchants and manufacturers, who were invested "with full power to uplift the money already subscribed, to endeavour to procure more subscriptions, to wait on the Committee of the Dispensary and to purchase a proper place for building a House."

Such a beginning is typical of the spirit of the Voluntary Hospital—the will to give both on the part of the physician and surgeon who contributed their skill, and of the churches and the community at large who never failed to ensure the necessary financial support and to furnish able and enthusiastic directors to carry on the management of the house.

## THE APPEAL FOR FUNDS

Having set up the Committee, efforts were at once redoubled to obtain the necessary funds. Some thousands of handbills were issued throughout the region, and an account of the project, together with plans, was dispatched to eligible persons in London and as far afield as the East and West Indies. The response was encouraging and included a letter from Bombay with a note for £50, which assured "The Managers of your new Infirmary that I highly approve of so humane an institution and that I feel myself much interested in its success. You have judged very rightly in electing for short periods the different officers of your hospital for I have observed where



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FIG. 3.—Dundee Halfpenny. The Infirmary with wings added in 1825 and 1827

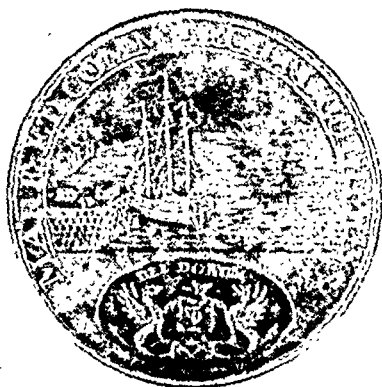


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FIG. 4.—Dundee Halfpenny. Reverse

allowed to continue for life or for a long time that the business falls at last under the direction of some individual who generally manages it ill." The ministers and elders of the Presbytery pled the cause in their respective pulpits before taking a collection, and other religious bodies gave active support. The Governors themselves set an example, like Mr James Pullar, the Deacon of the Bakers (Fig. 2), who gathered in the Overgate and is still remembered in the annuity which bears his name. Within a year £738 had been collected from all these sources, the fruit of a united and enthusiastic effort on the part of all sections of the community.

A chastely designed halfpenny or trade-token was issued in 1796, primarily to meet a local shortage of copper coin and also to stimulate interest in the hospital, which was then in building. It shows the central block with the two wings which were added in 1825 and 1827, thus completing the original plan (Fig. 3), while on the reverse a frigate lies berthed in the Tay, near the harbour of Dundee (Fig. 4).



*Photo by*

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FIG. 2.—Mr JAMES PULLAR, Burgess of Dundee. An original subscriber and governor  
From a portrait (1804) in the Board Room of the Infirmary





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FIG. 7.—Dr JOHN CRICHTON. Surgeon  
1798 - 1855. Consulting Surgeon  
1855-1860

From a portrait by Gibson in the Board Room  
of the Infirmary



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FIG. 8.—Dr JAMES ARROTT. Physician  
and Pathologist 1835-55

From a portrait by Stewart in the Board Room  
of the Infirmary



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FIG. 9.—The Old Infirmary as it is To-day



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FIG. 10.—The Reverend Principal FRANCIS NICOLL, D.D. Chairman 1806-20.  
Vice-President 1821-34

From an engraving of a portrait by Raeburn in the possession of the University of St Andrews

## THE BUILDING OF THE HOUSE

Meanwhile, failing an appeal to the Town Council to present a site, the Committee lost no time in selecting a piece of ground with a good southerly exposure, lying to the north of King Street where the original building, now Victoria Road School, still stands, and engaged Mr John Paterson, an Edinburgh architect, to complete the house according to his "genteel" plan at an inclusive cost of 1000 guineas; and indeed, he fulfilled his contract in such a workmanlike manner that he was voted a parting gift of £100. The accounts show that the building cost £1400, with furnishings amounting to a further £500.

The foundation stone was laid on the 17th June 1794, the Provost, Magistrates and Council walking in procession with the Governors who were also accompanied by the Deacons and the Nine Trades, the Masters and Brethern of the Four Lodges and the Box Master of the Fraternity of Seamen and his Fraternity. The erection of the building was regularly inspected and the workmanship approved, being better than any in progress in the town at that time, "any reports to the contrary having arisen through malice or ignorance."

## THE REGULATIONS

Much care was expended in drawing up the first Bye-Laws to govern the Charity, though little heed was paid to standing orders of meetings and the like; and these regulations in many respects resemble in substance, if not in detail, the rules which were only recently in force. The direction of affairs was vested in a President, Vice-President, Treasurer and Governors or Subscribers, who held their Court each quarter and, in the interval, delegated a limited authority to a Weekly Committee of eighteen Governors, the Directors, half of whom retired each year. As time went on, the expansion of the work demanded that increased powers should be assigned to the Weekly Committee on the spot and an opportunity was taken in the Royal Charters in 1819 and 1877 to effect this very necessary adjustment.

## THE FIRST PRESIDENT

Archibald, Lord Douglas, the first President (Fig. 5), held office for thirty years and his name recalls the celebrated "Douglas Cause," the most memorable Scottish civil suit of all time. It lasted for eight years and "no person who did not live at the time can form any conception of the agitation, the anxiety, the polemical spirit which it excited far and wide throughout the country" (Somerville: *My Own Life and Times*, quoted by Hume Brown). Lady Jane Douglas, after a secret marriage, gave birth in her fifty-first year to twins in Paris and, one of them, Archibald, survived to fall heir in 1761 to the extensive estates of his grandfather, the last Duke of Douglas.



As time passed, however, these regulations were interpreted with growing generosity and the scope of the service extended over a wide area of Eastern Scotland. "Every patient may be said to be kept gratis in the house" (1828). "Patients who have returned home in health may be examined by those who feel any interest in human suffering and they will find our witnesses from the Grampians to the Firth of Forth" (1825). This regional service was to some extent decentralised by the establishment of Infirmarys at Perth and Arbroath in 1838 and 1845, while the plans of the mother hospital had already been lent in 1836 to the Directors of Montrose Asylum, the parent body of the Infirmary of that town.

### THE WARDS

The wards were small with rather low ceilings and white-washed walls. They were furnished with ten beds apiece, some cast iron with metal or canvas bottoms, and others four-posters hung with curtains to exclude draughts. Good Scots blankets, stuffed stools and cushions for sore legs, a dressing-table, four-leaved screens, ward thermometers, bells, and lamps sufficient for reading in winter, attest a solicitude for the needs and comfort of the sick. Small chairs were also provided for little patients, who as a rule were admitted only as urgent cases for operation or when sick of a fever. Sheets were changed once a fortnight and the rest of the clothes once a month, if the patient had sores; nightcaps and stockings, if used, once a week. Donations of religious and instructive books were respectfully solicited for the inmates, but they, on their part, were not to presume to play at cards, dice or any other game, nor to smoke tobacco in the wards, nor to throw any dirt or any other thing over the windows. The roll was called every morning and evening, and all absentees reported to the Weekly Committee. These rules for in-patients, as well as those for the nurses, were hung in every room and ward and read when necessary "in order that none may pretend ignorance of them." The ministers of the town in turn conducted divine service each Sunday, with the help of a precentor who received sixpence for his help.

### THE NURSES

Nursing was of the Sarah Gamp order, with little or no distinction between nurses and servants, the latter being also known as supernumerary nurses. Besides domestic duties, such as cleaning the floor of sand by seven in the morning, they attended to medicines and diet and kept the wards aired. They applied poultices and fomentations, blisters and the like but did not dress wounds, nor attend the operation theatre. Their conduct was often in question and, though doubtless kind according to their lights, they had to be reminded from time to time that they must not neglect, insult or quarrel with the patients



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on any pretext whatever. They were also forbidden to interfere with each other or with the patients under each other's charge. The state of affairs, however, was no better elsewhere, as these early attendants of the sick were largely recruited from toppers and broken-down women who had difficulty in obtaining any other employment; and throughout the history of the old Infirmary the illicit use of ardent spirits—sometimes introduced by means of strings handed over the wall—continued to hamper the endeavours of the Board to establish an efficient service. As a counter-attraction trips were arranged to Broughty Ferry, “the Matron taking the nurses by turns and always under her eye and charge.”

Answering an advertisement which was affixed to the door of the Infirmary in March 1798, Mrs Farquharson was appointed the first nurse at 6s. a week with board, and a temporary watcher who resided at home gave her occasional assistance during the night. They were joined a little later by a second day-nurse, who received £12 a year with board, but “furnishing herself with tea and sugar.” While none of these persons or their immediate successors remained in their posts for any length of time, there is later ample evidence of great devotion to duty on the part of the nursing staff, especially during epidemics, and the surgeons also from time to time gladly acknowledged the debt they owed to them.

### THE DIETARY

The dietary list approved by the Committee in July 1798 is as follows :—

*Full Diet.*—Porridge and ale for breakfast. Good broth and flesh meat for dinner, and small beer for drink. Bread and ale, porridge or sowens \* with ale for supper.

*Middle Diet.*—Porridge or bread and milk for breakfast. Broth or greens and draught of small beer for dinner, with some flesh meat twice a week. Porridge, bread or sowens with milk for supper.

*Low Diet.*—Porridge or bread and milk for breakfast. For dinner, weak broth, boiled bread and milk, rice and milk, barley and milk, rice or bread pudding, breadberry, sowens. For supper the same as for breakfast :

which was “appointed to be hung in each of the wards.” To judge by the tenders accepted in the closing days of the old Infirmary, the food was at that time equally substantial and sustaining—wheaten bread, beef in shoulders, houghs and best pieces, London brown stout and intermediate ale. The malted liquors were the particular charge of the Matron who was occasionally directed to make a trial of the various descriptions of porter, before a contract was placed.

\* *O.E.D.* An article of diet formerly in common use in Scotland (and some parts of Ireland) consisting of farinaceous matter extracted from the bran or husks of oats by steeping in water, allowed to ferment slightly and prepared by boiling.

## FACILITIES FOR TREATMENT

There were ample facilities for bathing—hot, cold, shower and slipper baths forming part of the original outfit, besides a bathing machine acquired in 1802. These baths were also available for out-patients, and the machine was hired to the inhabitants of the town at the rate of sixpence a day. An electrifying machine cost £14.

In association with the Royal Humane Society an apartment was furnished at the docks with all the necessary means for the recovery of suspended animation, to deal with persons falling into the water whilst about the harbour; for it was considered that without such an apparatus the service would be incomplete, "cases requiring it being those that arise from suffocation, breathing foul air, strangling and falling into wells." After a time the outfit was transferred to a room in the Infirmary, in order that the victims might receive more adequate attention, but later it was taken back to the docks on the advice of the medical staff.

Special care had been bestowed on the construction of the operation theatre, with its roof lights and "circular doors finished with architraves." The lighting, however, proved faulty and new windows had to be broken out to remedy this defect. Forty pounds sterling was allotted for the purchase of surgical gear, including "tooth and womb instruments" and trephines; and some were acquired from retiring practitioners. A home-made set of silver catheters was presented by a local silversmith, and trusses were provided from a special fund. Except in cases of emergency, medicines were procured direct from London in order to ensure their freshness; and leeches too, the best spotted variety, costing 17s. 6d. a hundred, delivered free. A medical library consisted of the last editions of *The New Dispensatory*, *The Edinburgh Pharmacopœia*, and the *Pharmacopœia Chirurgica Londiniensis*.

## THE MILITARY OCCUPATION

The threat of invasion by Napoleon fell heavily on the country in the Infirmary's early days, and this is reflected in the many calls on the Committee to accommodate the sick of the successive companies which were quartered in the Barracks. Patients from the Sixteenth Regiment were at first admitted to the ordinary wards at the rate of 9d. a day for board and lodging but this arrangement soon broke down. Later it was decided to let "a ward, nurse, room and kitchen" to the Surgeon of the First Battalion of the Argyllshire Fencibles, at three guineas a quarter, payable in advance, the Committee agreeing to accept this sum on account of the regiment being fencible and not of the line, but "reserving power upon any of them proving disorderly to turn the whole out of the house." The anticipation of trouble was well founded, for shortly thereafter, in August 1800, it was reported

that the Apothecary had been insulted by the "centinel of the militia" and by the sergeant of the soldier's ward, who threatened to stab him with a bayonet, and that the surgeon's mate had also threatened to run him through the body. Happily the Commanding Officer tendered an ample and speedy apology, which "was sustained."

When the national crisis eased, the empty wards suggested the reception of paying patients and a resolution to this effect was unanimously approved; but for various reasons it could not be put into effect. A little later, after two years' deliberation, a ward was set apart for venereal patients, the rate being 5s. a week and "under the limitation that prostitutes are upon no account to be admitted, nor any person in any venereal state, unless such person is positively recommended as a proper object by two of the Committee, not professional men."

### THE SURGEONS

In rotation with his colleagues, the Attending Surgeon was in charge of all the patients in the house for a month at a time, so that they might experience a different regime at the pleasure of the doctor every thirty days. He was also required, after due consultation with the other surgeons and physicians, to undertake all operations during that period, an arrangement which very early led to a strange state of affairs, when the incumbent found himself unable to agree with his colleagues as to the necessity of performing an operation on a particular patient, in consequence of which, in the words of Mr Robert Stewart, the Senior Surgeon, "the operation was neglected, the patient dismissed, and the character of the house committed." It was therefore laid down that in future, when the Surgeon of the month thought fit to decline to operate, it should be his duty "to appoint any of his brethren concerned to operate in his stead, to which operation he shall be considered as his official assistant." For the time being, however, no attempt was made to extend the Attending Surgeon's tour of duty, and it was not until in 1808 and 1809 that it was prolonged to three and then six months. In 1817 the surgeons, now in office for three years, attended for twelve months at a time, the senior taking the first spell with the next senior as his assistant and successor, and the third conducting the vaccine establishment and following in his turn to the charge of wards.

Though the first physicians were not remunerated, each of the surgeons received a salary of £30 per annum and it was many years before they were regarded as purely honorary officers; indeed such a suggestion would hardly have been acceptable to any party. In 1840, for instance, when a letter was received from Dr John Thomson of Dumfries urging the abolition of these payments, the Committee observed that, though they were impressed by the zeal, energy and talent he had displayed in carrying out his views in Dumfries, they were not prepared to adopt the principle that medical officers should

receive no salary for their services, "conceiving that without payment there would be little responsibility and without responsibility little security for the regular and punctual discharge of duty." At the same time they saw no reason to augment the figure which had originally been assigned.

The physicians and surgeons were governors in virtue of their office but in the late thirties considerable doubt arose regarding the actual powers which they possessed. Some held that they were office-bearers in the full sense and so entitled to vote in the election of their colleagues, a claim based on a certain interpretation of the Latin of the first Royal Charter. After desultory debate, advice was sought from the Solicitor-General for Scotland and he gave as his opinion that the medical men were neither office-bearers nor directors and so had no voice in filling a vacancy, a decision which was accepted until the provisions of the second Royal Charter declared the Directorate open to the Consulting Staff.

#### DR CRICHTON

Among the surgeons the name of John Crichton (1772-1860) (Fig. 7) stands pre-eminent. Qualifying in Edinburgh in 1790 he had already operated for stone in the bladder and designed his own type of instruments before returning to his native town, as one of the original visiting staff. Dr Crichton's reputation as a lithotomist was soon established and his patients came from far and near, the worst sufferers arriving in beds suspended at their four corners to the posts of a cart; while a rail had to be erected at a proper distance around his table "to protect him from being pressed on too closely by the medical gentlemen who attend to see the operations performed." He was also widely called in consultation, at times as far south as the Border. Out of fully 200 cases, varying in age from two to eighty-five, we have it on his authority that only 14 died, the rest making excellent recoveries, while one patient is reported well and out of bed within three days (1840). Such a series is certainly unique, particularly when we recollect that he carried on all his work in the pre-Listerian era and, except in the last days of his active career, prior to the introduction of general anæsthetics. While Crichton attributed his skill, as Chiselden, to "a serenity of mind and a hand that never trembled," his success was largely due to the personal care he bestowed on his patients, particularly after operation. He had also great confidence, and contrary to accepted practice always "operated on every case whether considered by others favourable or not; neither have I found my reputation suffer thereby. On the contrary, I have in various cases experienced the satisfaction of seeing affections which were considered insuperable objections to an operation gradually give way after the pain and irritation occasioned by the original disease, have been removed." He was therefore a daring, courageous and distinguished surgeon and

merits a more prominent place in the annals of medicine than he has hitherto received. His term of office on the active list extended over nearly sixty years and was followed by appointment to the Honorary Consulting Staff, a period which embraced not only the life of the old Infirmary but also the first years of its successor.

### THE RENAISSANCE OF THE INFIRMARY

The year 1836 marks a renaissance in the history of the Infirmary. The internal arrangements were thoroughly revised. The Apothecary and his wife who acted as Matron, were retired on pension to make way for "a qualified medical man of education, experience and standing to superintend the house," from which he was forbidden to be absent after the closing of the gates at 8 p.m. These evening hours were to be employed in the new laboratory and other duties and, if possible, in contributing an occasional article to *The Edinburgh Medical and Surgical Journal*. A capable Matron "of active habits" was also appointed.

In the same year a medical charge was established under the care of the Attending Physician, and his position henceforth safeguarded from the encroachments of his surgical colleagues. For, despite an early undertaking that the classification of patients into Medical and Surgical Departments would be speedily observed, this pledge had been consistently shelved, and the physicians long denied their rightful place. The new arrangement proved most successful and for the space of the eight years which followed (1836-44) the work of the Infirmary, judged by the standards of the time, reached a high degree of excellence as a general hospital.

### DR ARROTT, PHYSICIAN AND PATHOLOGIST

Dr James Arrott (Fig. 8), step-brother of the pioneer physiologist, William Sharpey, entered on duty as Attending Physician in 1835, with high qualifications and an exceptionally wide experience. After graduating at Edinburgh, he went on a lengthy journey through Holland, Belgium and France, finally settling for a year at Paris, then at the zenith of its fame as a medical school, and there walked the hospitals with the most celebrated physicians of the day. So he saw much and learned many things which had not previously been taught in this country, and, all in due course, to the benefit of Dundee Royal Infirmary. Thus, for example, we hear of the wards being ventilated according to his plan and of his endeavours to establish the treatment of the patients on a sound, rational and scientific basis. "With the consent of the friends," he writes in 1840, "most of the bodies of those who have died were carefully inspected and, by comparing the symptoms observed during life with the alteration



which were found on the different organs after death and contrasting these with the effects of the remedies employed, I have endeavoured to draw fresh succour to the living from the dead." Thus, more than a century ago he created an active school of Pathology, long anticipating the recognition of this important subject on the part of the University. Dr Arrott was also a keen supporter of the movement to erect a new hospital and the completeness of the present building was largely due to the experience and care which, in association with Sir Robert Christison and Professor Syme, he bestowed upon the preparation of its plans.

As a clinician Dr Arrott devoted himself particularly to ailments of the chest, not only at the Infirmary but also at a special clinique for consumption and allied disorders which was opened in the Watt Institute, the first tuberculosis dispensary in the city. This bent is readily understood for, while he was in Paris, he had fallen under the spell of Laennec. Indeed a stethoscope used by Laennec himself was Dr Arrott's most cherished possession, and we too may have pride in the fact that the Infirmary enjoys this link with one of the greatest physicians of all time.

Dr Arrott's refreshing personality, however, aroused some opposition in certain quarters and this antagonism culminated in his failure to secure re-election as Attending Physician in 1848. Thereupon he issued a pamphlet attacking the practice which had lately grown up among certain Governors, of compiling lists which were signed in secret by their friends in favour of particular medical men. The dispute continued for a year but at next General Court Dr Arrott triumphantly carried the day, not only suppressing the irregularity of which he had been the victim but also securing his own re-appointment and leading to the resignation of the Chairman, who then held office. Dr Arrott's colleagues thereupon marked their approval by electing him Convener of the Medical Staff.

### THE SURGICAL DEPARTMENT

The reports on the surgical cases during this period, for example, in the year 1841-42, "when the accommodation, if not ample, was at least sufficient and well adapted for its purpose," are very striking—of 401 surgical patients, 323 were discharged cured, 47 relieved, 2 left irregularly and 21 remained, while only 8 died. "This has not arisen," says Mr Munro, the Surgeon, "in the slightest degree from any exclusion of patients in consequence of their being incurable nor from any urging of patients to leave the House when they were found to be approaching a fatal termination, a mode by which a medical attendant of a hospital may at any time bring the mortality within a convenient ratio." The number of operations was 49 in all, some of considerable gravity and extent, and "the result of the whole has been extremely gratifying, for all that have been operated on

during the year have recovered, having had no death after operation." This is certainly a most remarkable achievement in the days when wound fever was rampant with all its attendant evils; and it undoubtedly compares most favourably with any other hospital of the time. In this connection it should be mentioned that Mr Syme, the Regius Professor of Clinical Surgery in the University of Edinburgh, had continued on a friendly footing with the Infirmary since about 1836, when he had been accorded the unanimous thanks of the Board "for the valuable professional assistance he had immediately rendered the medical gentlemen in successfully operating in a difficult and dangerous case involving the life of two individuals"; and there is little doubt that he, who was soon to be acknowledged the greatest surgeon of the day, did much to inspire this promising school of surgery in Dundee.

#### A PATIENT'S APPRECIATION

Any account of the Infirmary during these fruitful years would hardly be complete without recording some expression of opinion on the part of the patients who were then being treated in the wards. Here is a letter received in 1844 :—

GENTLEMEN,

A short time ago I met with an accident which rendered necessary a very painful surgical operation and my friends urged me to go to the Infirmary where they said it could be performed more beneficially than at home. I felt no small degree of repugnance to leave my relatives and trust myself among strangers within the walls of an institution of which I had previously formed no very favourable opinion and it was reluctantly that I was prevailed upon to do so. It now affords me much pleasure to say that a short residence within the Infirmary dispelled all my fears and convinced me that the advice I had followed was decidedly the best that could have been given under the unfortunate circumstances. Nothing could form a greater contrast than the treatment I expected to receive and the gentleness and kindness shown towards me. Indeed, nothing that I could fancy necessary for my comfort in my situation was wanting. The unwearied exertions of all concerned with the establishment to alleviate my suffering both during the day and during the night, the cleanliness and comfort of all the Departments of the house and the means used by nutritious aliment and otherwise to accelerate my recovery, have left a sense of gratitude on my mind which will not be easily effaced. To Mrs Mitchell, the matron, and Mr Ross, the house surgeon, in particular, my warmest thanks are due for the urbanity and indefatigable exertions to forward the end for which I became an inmate of your invaluable institution. I am certain that, if the wealthier portion of the community were aware of half of the benefits conferred on the humbler portion of the fellow townsmen, the funds of the Infirmary would be in a more prosperous state than they are.

I am, Gentlemen,

Your very humble servant,

JOHN PEEBLES.

## THE CLOSING YEARS

The closing years of the old Infirmary were marked by the super-human efforts which were made to cope with the outbreaks of infectious diseases which were then devastating the town. In 1847-48, for example, 1264 cases of "typhus" fever (deaths 205), 1840 of "epidemic" fever (deaths 30), 21 of smallpox (deaths 2) and 15 of dysentery (deaths 8) were admitted to the wards. The death-rate from these conditions was therefore very moderate, in striking contrast to the toll exacted by malignant cholera, "that dreaded and fatal scourge," which visited the town the next year and affected fully 1600 persons. Three hundred and four of them were admitted to the Infirmary and though 173 of these died—a shocking mortality but not greater than elsewhere—it says much for the routine observed in the wards that Dr Webster was able to report: "Without entering upon the question as to whether cholera is or is not contagious, I consider it right to record as an historical fact that, notwithstanding the large number which was received and treated within the grounds of the Infirmary, not a single case of the disease manifested itself among the medical officers, students or domestics of the establishment, nor among the patients sojourning there for the cure of other diseases!" a statement which might be expected of a well-regulated hospital, since those in close contact with cholera are not readily affected, if proper precautions are observed.

The introduction of general anæsthetics, too, in 1847, first of ether and then of chloroform, did much to hearten the efforts of the medical staff in these dark days.

The old Infirmary was sold (for £3000) in 1857 and ultimately acquired by the School Board. Though modified to suit their purpose, the building still presents the dignified exterior of a substantial Scots building of the latter part of the eighteenth century (Fig. 9).

## THE MEDICAL SCHOOL

From the earliest days instruction had been given to "respectable" young men who purchased their tickets as medical students; and later a system of indenture between the Board and these apprentices also prevailed. The Medical Staff, however, had long been anxious to have the Infirmary recognised by the Royal College of Surgeons of Edinburgh and were therefore much gratified to receive a letter in 1843 from the President of the College, Mr Andrew Fyffe, informing them that their course had been approved "as a part of the hospital attendance imperative on those studying for a Diploma from the College, so long as the average number of patients in the Infirmary continues to be eighty which is the number specified by the College in its regulations."

In passing it may be noted that the first contact with the University



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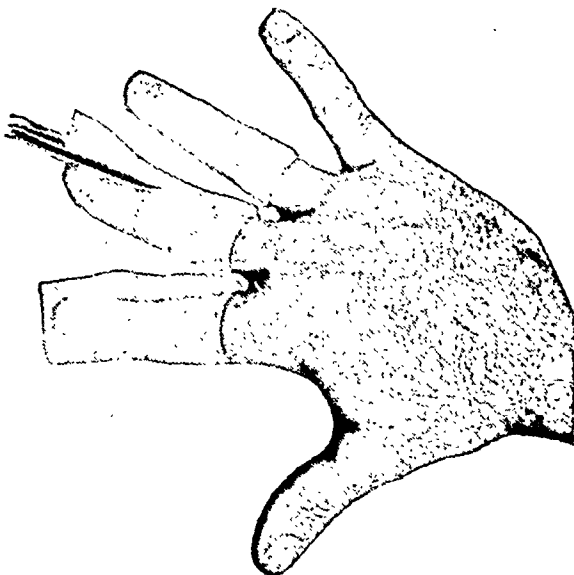
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MEDICAL DEPARTMENT

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of St Andrews came about in 1857, shortly after the opening of the new Infirmary, when permission was sought to use the wards for conducting a bedside examination in the case of those candidates for the Degree of Doctor of Medicine, who had acquitted themselves with credit in the first two days' examination and were then allowed to compete for honours by testing their practical knowledge of medicine. At the same time an assurance was given that the young men would do the patients no harm, as well as a promise of a moderate subscription to the funds. This arrangement seems to mark a sincere effort on the part of the University to make its degree in medicine more reputable than had hitherto been the case.

### FINANCE

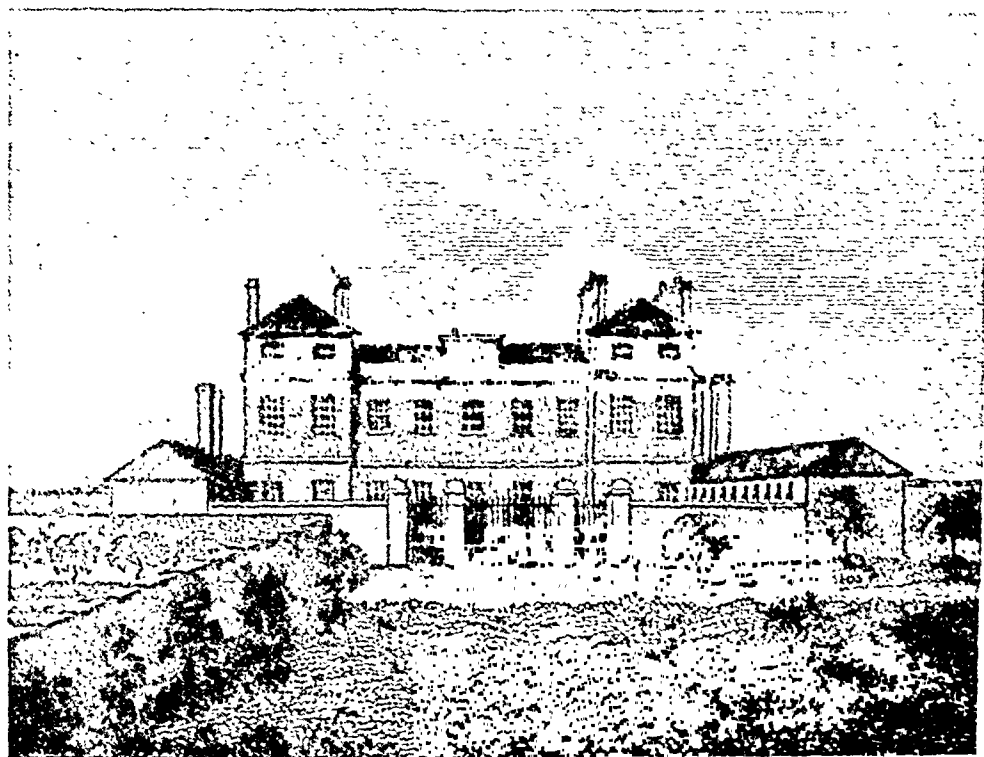
From the beginning the income of the Infirmary was derived from subscriptions, donations, church collections, public works and investments, sources of revenue consistently maintained throughout the years, though differing in their proportions with the altered conditions of the times. Some particular items, of course, have long since disappeared, for example the fines imposed by Courts, as on one occasion when the General Commissioners of Police forwarded penalties amounting to £123. Social events were by no means neglected, as the grand balls and the Siddons' benefit night in 1811. The workpeople in the mills too, then as always so well disposed to the house, from time to time gave up as much as a day's pay for its support. Half the proceeds of a discussion on socialism realised the sum of 54s. 6d. in 1841.

As required by the Bye-Laws, a sermon was preached in the presence of the Governors and a collection uplifted, immediately before the annual meeting in June. The Magistrates, Governors and public bodies assembled in the town hall at 10 o'clock and then moved off in procession, headed by a band, to the church. Many eloquent addresses were delivered, though the congregation was specially impressed in 1811 by the Reverend Francis Nicoll, D.D. of Mains and Strathmartine, when the collection amounted to £68, 13s. 2½d., less fully £3 expenses for the procession. The Court followed the service, and then at 4 o'clock, "the Governors, together with the clergyman who preached before them, the Magistrates and other inhabitants, who may be inclined to promote the interests of the charity," dined together at one of the inns. The Provost presided, supported by a croupier and six stewards and upwards of a hundred guests. Unfortunately, it was deemed expedient in 1818 to abandon the procession, as "the benefit resulting to the Infirmary bears no proportion to the evils which these exhibitions produce by occasioning idleness and dissipation, and thereby injuring both the means and the morals of the labouring classes." Nevertheless, the Committee were very reluctant to abandon the holiday spirit, for four years later

they arranged "to borrow the musical instruments belonging to the local militia for the use of the band which is to attend the Governors at their annual meeting in June." Next year the procession was finally discontinued "in consequence of the disorder which it causes in the town."

#### THE REVEREND PRINCIPAL FRANCIS NICOLL, D.D.

The Reverend Dr Nicoll (Fig. 10), whom we have just mentioned, was typical of the benevolent spirit of his time and served as Chairman on ten occasions between 1806 and 1820, including the year 1809



*Photo by*

*Watt & Sent*

FIG. 11.—Dundee Royal Lunatic Asylum

*From Dundee Delineated (1822)*

when he, like his predecessor Dr Small, was chosen Moderator of the General Assembly in recognition of his leadership of the Moderate Party and of his untiring efforts to extend the benefits of the Widows' Fund of the Church of Scotland. This interest in finance likewise proved a valuable asset to the Infirmary in the anxious days before any reserve had been accumulated; and there are records of many gifts received by his hand, besides a picture of his presiding at a meeting in 1810, when the poor's box, well lined with plate-iron, was duly produced. "A blacksmith was ordered to pick the locks and, having opened it in the presence of the Committee, there was found in the box ten shillings and ninepence half-penny sterling, which was delivered to the Treasurer."

Dr Nicoll also took a very prominent part in the establishment of the Lunatic Asylum.

His active association with the Infirmary ended on his appointment as Principal of the University of St Andrews, and his success in that office was due perhaps in some small measure to the experience he had gained in the affairs of the Board and in his contacts with the early medical staff, whose problems were readily resolved by his kindly and judicious approach.

### DUNDEE LUNATIC ASYLUM

The need of provision for the insane had impressed the Committee as early as 1796 when they felt obliged to lodge a lunatic for a short time in one of the low rooms of the Infirmary then in course of erection, and they immediately planned to add a wing to the house to accommodate these cases. The appeal for funds, however, was very successful and it was then decided to build another institution on the Craigie estate at the north-east of the town on a site of three acres, which gave sufficient room for airing-grounds. Advice was sought from Mr Stark, an Edinburgh architect, who had specialised in this branch, and he drew up a model plan incorporating all the improvements of the day which "met with the most unqualified approbation of the best judges." The foundation stone was laid by Lord Duncan in 1812 and the House (Fig. 11) informally opened in 1820, after its management had been handed over to a separate Board in terms of the Royal Charter of the previous year.

### TRIBUTE

This short account is a tribute to the benevolence, initiative and skill of those who established the Dispensary and the Infirmary, as well as planned the Asylum, at Dundee in the course of the eighteenth century, an age distinguished for its moderation and philanthropy and which, here as elsewhere, gave sober expression to its feelings in the foundation of the Voluntary Hospital "just as the age of Faith had sung its soul in the stones of cloisters and cathedral aisles" (Trevelyan : *English Social History*, p. 345); and likewise to all who continued to maintain this generous tradition and to give faithful service over the past one hundred and fifty years.





## A SEVENTEENTH CENTURY CASE OF POLIOMYELITIS

By WILLIAM J. MALONEY, M.D., LL.D., F.R.S.E.

IN the third book of *L'orthopédie*, Nicolas Andry (1658-1742), the father of that art, recounts the case of a child, who had never an ailment, until the use of his legs was lost at the age of six, when riding on the shoulders of his elder brother.

For some time this game had delighted the child and done him no harm, when, one day in 1699, while riding as usual, he was seized with weakness of both legs. The alarmed parents at once had recourse to the remedies they thought best. Presently the left leg recovered, but not the right.

Andry's account makes no mention of sphincter, sensory, or trophic trouble; and no hint of accident. A sudden paralysis of this sort, in a previously healthy child, with a prompt recovery of one leg, and residual paralysis in the other, suggests poliomyelitis. In this instance, Andry attributes the paralysis to strain ("Jambes paralytiques par effort"). Riding astride the brother's neck, the little lad was thought to have held on too tightly with his legs, thus daily overstraining their muscles till these finally "gave," like the overstretched string of a bow too often bent.

This explanation, though given by Andry, was not his. He never saw the case, and knew of it only from a brochure by M. Salzmann of Strasbourg.

There were then several learned men of that name and place. The author of this brochure was Jean Godfroy Salzmann (1672-1738). A graduate of Strasbourg, he studied at Paris in his youth, and toured the medical schools of Germany and Switzerland, before settling down in his native city. There he occupied, in turn, the chairs of anatomy, surgery, and pathology; served as dean of the medical faculty, and wrote many learned dissertations. Of these, Dezeimeris lists thirty-one, the twenty-ninth, being the report of the case that Andry recounts.

Andry was an editor of the *Journal des Sçavans* (1665-1753), which, according to Dr Douglas Guthrie, was the first scientific periodical in the vernacular. A classical scholar from his tonsured days, a royal censor in the reign of Louis XIV, and doyen of the Paris medical faculty, Andry made French digests of the Latin dissertations that reported the remarkable and strange in current medicine. From the digest of Salzmann's dissertation, made for the *Journal*, came the more condensed account of the case which later appeared in *L'orthopédie*, under the heading "Jambes paralytiques par effort."

Every month the *Journal des Sçavans* was issued at Amsterdam as well as at Paris. Andry's original abstract of Salzmann's monograph was published, unsigned, in the December number of the Amsterdam issue in the year 1735.

There the title page of the monograph was rendered "Dissertation sur un manquement de plusieurs muscles du pied.\* Par Jean-Godfroy Salzmann, Docteur en Médecine. A Strasbourg, de l'Imprimerie de Jean-Henr. Heitzius, 1734."

The Amsterdam text of Andry's abstract reads in English: "One cannot too highly commend those who take the trouble to publish the exceptional and curious facts they observe in medicine, anatomy, and other sciences. In 1718, there was reported a rare fracture of the frontal bone, which, uncovered the dura mater; and which the patient had survived for forty years. In *Ephémérides des Curieux de la Nature* (Centur. X, Observ. 48), there is an account of an infant that was forty-six years in its mother's womb, encased in its calcified caul, as in a casket.

"These things are amazing, especially the latter, which may well be considered unique. The case described in the present work may give less cause for wonder. Nevertheless, it seems sufficiently unusual to merit the attention of the learned.

"M. Salzmann, who reports it, declares he has never seen or read anything like it. Here it is, stripped of a great many extraneous facts, which, in M. Salzmann's dissertation, tend to obscure it.

"A man, lame of his right leg, had walked with great difficulty for many years. At the age of 40, he died of a fever; and the affected leg was then dissected under the direction of Professor Salzmann, of the medical faculty of Strasbourg University. He found that most of the muscles were gone, and that those remaining scarcely retained even their normal outline. Among the muscles that had disappeared, M. Salzmann names the gluteus minimus, the quadriceps, the crureus, the tensor of the fascia lata, the sartorius, the gracilis, the popliteus, the tibialis posticus, and almost all of the soleus.

"There was no muscle on the sole of the foot, but only fat.† The short flexor of the toes; the lumbricales; the interossei, both internal and external; together with the abductors and adductors of the toes—all had disappeared, leaving the sole without flesh.

"Among the muscles of which traces persisted, the gluteus maximus was still muscular below, but not above, at its origin from the sacrum and ilium. The gluteus medius was half-fleshy behind, but merely fatty and tendinous in front. The only remaining muscle fibres of the vastus externus were in its lower part; while all that were left in the vastus internus made a small bundle as thick as a little finger, and about five finger-breadths long. The rectus had greatly shrunk, and only a few muscle fibres were seen in its upper part. The triceps was

\* In this title Andry uses "pied," not "jambes" as in his book.

† Cf. the "paralysie atrophique graisseuse de l'enfance," of Duchenne.

much smaller than usual, especially its central part. The biceps had scarcely half the usual number of fibres, and neither the semitendinosus nor the semimembranosus had more. The gastrocnemius, in its middle and posterior part, still possessed a strand of muscle, consisting of very thin, stretched-out fibres; and the small plantaris was much smaller than usual, for its muscle fibres were very few.

"To these, M. Salzmänn adds the tibialis anticus, and the peroneus longus, each of which disclosed only an inconsiderable muscle bundle; the long common extensor of the toes which showed more than the tibialis anticus, but still many fewer fibres than normal; the short common extensor, of which only the innermost of its four parts remained; and the long common flexor of the toes, which was only half the usual size.

"But he notes that among the flexors of the thigh, the iliacus and the psoas were intact; as were also the pyramidalis among the rotators; and the pectineus, among the adductors. He says the same of both the flexor and the extensor of the big toe; as well as of the extensor of the little one.

"M. Salzmänn makes the following observations that should be noted: 1. The spaces once occupied by the muscles, which had disappeared in whole or in part, were filled with a thick fatty substance, like that found in the encysted tumours, called steatomas. 2. The fleshy fibres of the affected leg, not merely of those muscles which were reduced to a remnant, but also of those which were conserved intact, were pale, and more like fibres of tendon than of muscle. 3. The disease affected not the origins or insertions of the muscles but their bodies, for most of the tendons were normal, not only in colour and length, but likewise in thickness.

"Before entering into all this detail concerning the muscles, M. Salzmänn describes the use the patient made of them: First, the right foot, which was not merely limp but paralytic, was swung outwards, in a semi-circle, as if it were artificial. Being practically devoid of muscular power, the right foot and leg moved not of themselves but solely and clumsily in consequence of movements of the thigh. The patient was able to stand on the right foot, but when he wished to go from one place to another, he could not, without the aid of a cane. In addition, the front of the shinbone was turned out; the front of the foot, in; and the middle of the sole was retracted to form a considerable cavity. The thigh flexed easily; and also without undue effort, the right leg might be put over on the left, but it could be neither extended nor abducted.

"While the patient lived, the source of his trouble could not be ascertained. After he died, doctors were able to look inside the paralysed leg, and to uncover the state of its muscles. As this did not suffice wholly to clear up so obscure a condition, and, moreover, failed to disclose the origin of the muscular defects, further inquiries were made.

"At first it was thought that the lack of muscle might arise from a fault of development. Apparently favouring this idea was the patient's insistence that his difficulty in walking had dated from infancy, and that he had never heard his leg had been hurt by a blow or otherwise. So for a while the condition was thought to be intra-uterine, until it was proved to be post-natal.

"Several persons were found who had known the patient in his earliest childhood. These affirmed that from his first to his sixth year, he was as agile on his right leg as on his left. From them it was learned that he then took to riding on the shoulders of his big brother, with whom he usually played. He sat astride the neck, with his legs hanging down in front of the chest, one on the right of the neck, the other on the left. For a time this was apparently harmless. But one day, on repeating the ride, the child experienced an attack of considerable weakness in his legs. The parents used liniments, ointments, volatile oils, and warm mineral waters, as well as stimulating baths prepared either from ants, or from the lees of red wine. By such means they soon succeeded in curing the left leg. But for eight long years the right leg remained helpless. The parents never ceased their efforts. They continued assiduously to apply the remedies. And, at last, their perseverance was rewarded to the extent that the lad became able to walk with a cane.

"The immediate problem is to determine the cause of the muscular defect. M. Salzmann considers this question at length, but what he says may be stated here in a few words. He claims that the true cause of the child's trouble was the excessive strain on its muscles when riding with a leg on either side of the brother's neck: and that the effect of this strain was to cause the taut muscles to 'give,' thus paralysing the legs and rendering them useless. M. Salzmann's presentation of his theory does not readily lend itself to abstracting, and should be examined in his Dissertation.

"Here we merely mention, however, that, to illustrate his idea of what happened, M. Salzmann uses the comparison of a bent bow, too tightly strung, of which the taut cord at last yields, losing all its strength. On this analogy, he tries to show that the fluids required for nourishment could not enter the taut muscles; that the nerves were compressed and obstructed; that the circulation was deranged; and that the whole brain as well as the spinal cord was affected.

"Because of the inaction of the muscles and nerves, much thick matter was lodged in various regions of the leg, and gathered into corrosive, putrefying accumulations which gradually ate away the several muscles, in whole or in part. . . .

"But why was the left leg cured rather than the right, though both got the same treatment? M. Salzmann explains this very naturally in the following way: Riding astride, the child bore on the right more than on the left leg; which is very likely. And it is easy to understand that the strain being greater on the right leg, the

blood vessels in it were more compressed, narrowed, and obstructed. Although volatile remedies were applied equally to both, they were less readily carried away on the right, and tended to linger there unduly. Too active local applications often hurt more than they help. They are apt to disperse the finer, more nutritive humours; and to leave only the coarser, the less sustaining and strengthening. Among the topical applications used in this case, M. Salzmann mentions *eau de vie* (brandy).

“ ‘ *Hiscæ causis addimus, quod a discutientibus et spirituosis, præ primis spiritu vini, aquis etiam thermalibus et nervinis, particulae humoris alimentarii subtilioris discussæ et dissipatæ fuerint, relictis crassioribus nutritioni minus aptus . . .* ’

“ It is not necessary here to justify the translation of *spiritu vini* as brandy. Most people know that *spiritus vini*, without the adjective *rectificatus*, signifies not spirits of wine but brandy, or *eau de vie*. As this remedy is daily abused, often it might more aptly be called ‘*eau de mort*.’ In conclusion, this case, on which M. Salzmann has written his Dissertation, shows how important it is to bear in mind what may happen to children either carelessly carried, on the arm or otherwise; or subjected to violent strain in any part of the body.”

M. Salzmann’s dissertation was dated Strasbourg, 30th December 1734 and entitled, *Sistens Plurium Pedis\* Musculorum Defectum* (“On the Disappearance of Most of the Muscles of the Leg”).

About the onset and course of the paralysis, and on the condition of the dissected muscles, the dissertation records little of moment that Andry has omitted from the abstract. Discarded by him as obscuring the case was mainly material that Salzmann had gathered from the works of Cowper, Morgagni, Santorini, Valsalva, Winslow, and other noted anatomists, on structural variations in man. This material includes monstrosities, and skeletal anomalies, as well as muscles that were absent, or were atypical in origin, course, insertion, or number; and was probably assembled while the patient was insisting that the leg had been lame from infancy and had never been hurt.

Also ignored by Andry was a discussion on palsy. Salzmann considered the word not merely in the general sense in which Galen uses it (“*L. 1. de caus. sympt.*”), but also as it is defined by Boerhaave in aphorism, 1057.† This he quoted: “A palsy is that loose unmoveableness which is not superable by any endeavours of the will or vital power; feeling is sometimes wholly lost at the same time;

\* “*Pes. The leg (late Latin): in, phrase, pedem frangere, Aug. Civ. Dei, 22. 22, 3; id. Serm. 273, 7.*” *A New Latin Dictionary*, by Lewis and Short, Oxford and New York, 1886.

† Boerhaave’s aphorisms served as a textbook for John Rutherford’s class when he was professor of the practice of physic at Edinburgh University. Professor Rutherford was Sir Walter Scott’s maternal grandfather. When Scott was attacked by poliomyelitis in February 1773, he was attended by Rutherford, who probably pondered aphorism 1057, just as Salzmann did.



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sometimes that remains in small degree with a numbness and a slight pricking sensation."

The "insuperable unmoveableness" from which his patient suffered, Salzmann vaguely surmised was caused by what would now be called a lower motor neuron lesion. At least, he seems to suggest that it did not arise from "the uppermost part of the nerves." Seeking light on the condition, he collected cases of spinal caries and dislocated vertebræ, and mentions that in these not only were the legs paralyzed, but the bladder and rectum, too.

Then (p. 23) he cites "Mich. Etmullerus [1644-1683], Praxis L. 2, S. 3, C. 3, Art 3," where it is written: "A true, formal palsy affects chiefly the moving faculty, and if the nerves are not much touched, the sense of feeling remains. . . . The particular apoplexies are retainers to the disorders of the brain and spinal marrow; whereas palsies follow another set of diseases, as the scurvy, hypochondriac and colic fits [lead], and excessive drinking. In the former, the original and uppermost parts of the nerves are chiefly affected . . . but in the latter that part of the nerve which accompanies the muscles of the place is principally injured, and accordingly external applications are confined to that quarter. The former deprives of sense and motion, the latter oftentimes retains the sense, and is molested with pains . . . the latter relents now and again and 'tis not so hard a matter to compass its cure."

Andry refers to the left leg as cured,\* while Salzmann describes it only as improved.†

The dissertation does not tell how far this improvement fell short of complete recovery. But whatever its state, the left leg was the cripple's mainstay. With the aid of a cane, it enabled him to walk, and even to climb a stair if the steps were low. But he could not go far. Every once in a while, he had to sit down and rest. And adapting his life to his limited activity, he became a printer.

His sedentary habit and fondness for food early made him obese. About the age of thirty his weight began to restrict the short range of his walking. Thus curbed, he grew irritable and depressed. Then he took to drink. Ten years of this existence reduced him to such a state that a fever he caught when he was forty quickly ended his tragic life. The dissection took place on 12th March 1733.

Salzmann seems to have seen the case only in this last stage. The cripple had then forgotten, with the aid of brandy, the commencement of his trouble. From hearsay, Salzmann tells of the playful big brother and the devoted parents. Presumably they were dead in 1733, for he does not quote them. The parents are last mentioned when the lad, after eight years of their treatment, began to walk, in 1707. He was then fourteen. On their death, he may have moved into

\* "Les parents . . . vinrent à bout de guérir la jambe gauche" (loc. cit., p. 493).

† "Pes sinister meliorem in statum redactus est" (loc. cit., p. 16).



Strasbourg to work at his trade. In any event, when he came at last to Salzmann, he had long been absent from the locality where he was stricken. Yet, he still remembered its name, and it was evidently near enough to induce Salzmann to seek there the "several persons" he found, "worthy of credence," who had known the cripple as a healthy agile child. Hence, it would not be far wrong to refer to this as a Strasbourg case, though it may have happened in the country nearby, and not in the city itself.

Concerning the season at which the attack occurred in 1699, the dissertation says nothing.

The patient complained to Salzmann that the right leg, besides being weak, had spots on it, which came and went; at times were livid, and at times, dark red; were often painful, and occasionally ulcerated (p. 17). Such pains as troubled the right leg in 1733, may have come with the years, from the prolonged strain of walking with atrophied muscles: and this heavy strain, together with a decade of drinking, also may have induced the slight vasomotor and trophic changes which caused the sore spots to come and go on the skin.

Besides these minor troubles, which may have been belated, Salzmann found the right leg greatly wasted; shorter than the other ("*extremitas affecta brevior altera*"); extremely weak; and easily moved, or twisted, in any direction. Moreover, it was defective in feeling, and lacked its natural heat ("*caloris nativi defectu*").

Salzmann's account of the onset and course of the paralysis, his description of the patient's gait and movements, his clinical notes on the wasted right leg, and his brilliant report of the dissection of its muscles, make clear to modern readers that the original attack fell mainly on the motor cells of the anterior horn of the lumbo-sacral enlargement, on the left side as well as on the right. On the left, the lesions being largely reversible, the leg soon improved. On the right, permanent destruction took place at levels (L 2 to S 2) below the psoas and iliacus innervation and caused almost complete disappearance of some muscles, with partial wasting of others, while a few escaped undamaged. If the sensory loss did not arise from a superadded alcoholic neuritis, then the lesions on the right were not confined to the anterior horn but had spread to the posterior also.

Diseases may change with the times as much as the words that are used to describe them. In living experience, poliomyelitis has changed from an endemic disease to a universal scourge. During its endemic period, the disease appeared in a standard, classic form, perhaps because other types now known then passed unrecognised.

Among the many manifestations of the epidemic poliomyelitis of the twentieth century, this classic form still prevails. At the commencement of the nineteenth century, it was known in Scotland, England, Germany, Italy, Norway, Sweden and France. In the eighteenth century it was noted in England (1798, 1789), Germany (? 1782), and Scotland (Edinburgh, 1773). And in the seventeenth

century, Salzmann has established its presence near Strasbourg (1699).

As the disease did not arise *de novo* in its classic form while this child was riding on his brother's shoulders, and as this great old clinician describes it in terms still easy to comprehend, research should readily uncover earlier cases, and give much-needed light on the history of this scourge. Meanwhile, Salzmann's case demonstrates that in the changing world of poliomyelitis, invasion by its virus has excited a stereotyped human reaction, the classic pattern of the disease, which has now been recurring in recognisable, and often identical, form for at least 250 years.

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## THE EFFECTS OF THIOURACIL UPON CLIMACTERIC HYPERTHYROIDISM

By A. W. BRANWOOD, M.D., F.R.C.P.E., M.R.C.P.

MUCH more is now known of the antithyroid compounds than in 1928 when Chesney *et al.* noted the goitrogenic action of a cabbage diet on rabbits. Marine *et al.* in 1932 demonstrated that the effect of this diet was caused by its high nitrile content. In 1941 the Mackenzies showed that a similar effect occurred in animals following the administration of sulphonamide compounds, especially sulphaguanidine. It remained for Astwood to apply this knowledge to the treatment of thyrotoxicosis and in 1943 he published the results of his studies on the effects of thiourea and thiouracil in Graves' disease.

The results of thiouracil therapy in the control of hyperthyroidism have been startling, and nowadays it is the treatment of choice in the majority of cases of thyrotoxicosis.

Many cases of hyperthyroidism have been seen in the Medical Out-patient Department of the Royal Infirmary, Edinburgh, during the past two years. Some of them, for various reasons, were not admitted to hospital but were treated at home and reported for re-examination at definite stated intervals. The majority of the latter have shown great clinical improvement under thiouracil therapy. Certain patients, however, although having clinical manifestations suggestive of thyrotoxicosis, when treated with thiouracil did not show the expected response.

### CASE MATERIAL

(1) A woman aged 40 years had complained of nervousness, sweating and palpitation for three months. Her periods had been regular. On examination she had a flushed, warm, soft, moist skin, a fine tremor of the hands and a tachycardia of 102 per minute. Her blood pressure was 140/60. There was no enlargement of the thyroid gland and no exophthalmos although her eyes were unduly bright and there was some slight subconjunctival oedema. Her weight was 9 stones. She was treated with phenobarbitone, grs.  $\frac{1}{2}$  b.i.d. and thiouracil 0.2 gm. t.i.d. for three weeks. When she was seen at the end of that time her pulse rate was 95 per minute and her blood pressure 140/60. She still had a warm moist skin and the eye changes were similar to when she was first examined. Her weight, however, was 9 st. 6 lb. She returned a month later, having been given a maintenance dose of thiouracil of 0.1 gm. daily and the phenobarbitone stopped. The physical findings were unchanged but her weight was now 10 stones. She reported thereafter at monthly intervals for a further four months. On each occasion her weight had increased, 10st. 4 lb., 10 st. 8 lb., 10 st. 13 lb., and 11 st. 2 lb. She maintained she felt no better and still had palpitations while the sweating and nervousness remained. Her pulse rate was now 95 per minute, the blood pressure 140/64.

The fine tremor was still present, the eyes were slightly prominent and very bright, and the thyroid gland had become definitely enlarged.

(2) A woman, 43 years of age, had suffered from palpitations, sweating and nervousness for six months. She thought she had lost a little weight. Her periods were regular. The skin was warm and soft, there was a fine tremor of the hands but no palpable enlargement of the thyroid gland. Her pulse was 104 per minute and the blood pressure 146/70. Her weight was 9 st. 2 lb. The eyes were very bright and slightly prominent. Phenobarbitone grs.  $\frac{1}{2}$  b.i.d. and thiouracil 0.2 gm. t.i.d. were given for three weeks. At the end of that time her pulse was 90 per minute, blood pressure 140/70, the skin remained warm and moist, and she stated she felt just as nervous as before. Her weight had, however, increased to 9 st. 9 lb. The tremor of the hands was still present, the eyes were unchanged, and there was no enlargement of the thyroid gland. The thiouracil was continued for a further week and then reduced to 0.1 gm. daily. The phenobarbitone was discontinued. She reported again in a month's time. Her weight had increased to 10 st. 1 lb. The other signs and symptoms were unchanged. She was examined monthly for four months and her weight at the end of that time was 12 stones. The thyroid gland was enlarged, her hands showed a fine tremor, the skin remained warm and moist and there was definite exophthalmos.

(3) A female patient, aged 45 years, gave a history of nervousness, sweating, palpitation and dyspnoea for several months together with a loss of weight. Her periods were regular. Examination revealed an excitable woman with a warm elastic skin, moist palms and a definite tremor of the hands. Her pulse was regular, rate 100 per minute, the blood pressure was 150/70. Mild exophthalmos was present and her weight was 9 st.  $7\frac{1}{2}$  lb. There was no enlargement of the thyroid gland. Thiouracil 0.2 gm. t.i.d. and phenobarbitone grs.  $\frac{1}{2}$  b.i.d. were given and she was seen again in a month's time. She was 10 st. 2 lb. in weight, her eyes were even more staring, and the tremor, sweating, and tachycardia with increased pulse pressure persisted. She was given 0.2 gm. of thiouracil daily and she was examined again a month later. Her weight on this occasion was 10 st. 13 lb., the pulse rate was 90 per minute and the pulse pressure still increased. Her eyes were still prominent, the skin had the same texture and she was still nervous. She reported monthly for a further three months. At the end of that time her weight had increased to 11 st. 11 lb., there was definite exophthalmos, and although the skin was dry she complained of it feeling hot. She was still nervous and her periods were now irregular.

(4) A woman aged 42 had suffered from nervousness, sweating and loss of weight for three months. Her periods were regular. On examination her pulse rate was 90 per minute and the blood pressure 150/80. She had a fine tremor of the hands, the skin was warm and moist and slight exophthalmos was present. She weighed 8 st. 10 lb. There was no enlargement of the thyroid gland. Thiouracil 0.2 gm. t.i.d. and phenobarbitone grs.  $\frac{1}{2}$  b.i.d. were taken for three weeks. She then weighed 9 st. 2 lb. The pulse was still 90 per minute and the blood pressure 144/80. The tremor persisted and the exophthalmos was still present. She stated that she felt no better. The thiouracil was reduced to 0.1 gm. daily, and she was seen again a month later. She now weighed 10 stones, was very nervous, sweated a great deal and had attacks of palpitation. The pulse was regular, rate 90 per minute, and the blood pressure 150/80. She reported monthly for a further three months.

At the end of that time her periods were irregular, the weight was 10 st. 6 lb., exophthalmos was very noticeable, the skin was warm but dry, the pulse still fast and the pulse pressure still increased. The thyroid gland was enlarged.

(5) A woman, 38 years of age, had suffered from sweating, dyspnœa and palpitation for four months. Her periods were regular and she thought she had lost weight. She was a nervous woman with slightly prominent and very bright eyes. She had a fine tremor of the hands and the skin was soft, warm and moist. Her weight was 9 st. 1 lb. There was no enlargement of the thyroid gland. The pulse rate was 90 per minute and the blood pressure 148/74. Phenobarbitone grs.  $\frac{1}{2}$  b.i.d. and thiouracil 0.2 gm. t.i.d. were prescribed. At the end of three weeks she still had a tachycardia with an increased pulse pressure. Her weight was now 9 st. 9 lb. The eyes remained slightly prominent, the conjunctivæ still glistening, the skin soft and moist and the tremor of the hands persisted. The thyroid showed no enlargement. A maintenance dose of thiouracil 0.1 gm. daily was ordered, and she reported monthly for four months. She then weighed 11 stones, the thyroid gland was palpably enlarged, the skin was warm and still moist, her pulse was 90 per minute and the pulse pressure 72 mm. The tremor persisted, the eyes remained prominent and she maintained she felt as nervous as before. Her periods were now irregular.

(6) A female patient aged 42 complained of tiredness, dyspnœa, loss of weight and sweating for four months. Her periods were regular. She weighed 9 st. 2 lb. and had very slight exophthalmos with glistening conjunctivæ. Her pulse rate was 100 per minute and the blood pressure 150/70. There was no enlargement of the thyroid gland and no tremor of the hands although the skin was warm and moist. Thiouracil 0.2 gm. t.i.d. and phenobarbitone grs.  $\frac{1}{2}$  b.i.d. were prescribed for three weeks. Her weight had then risen to 9 st. 10 lb. and the other signs and symptoms were unchanged. The thiouracil was reduced to 0.1 gm. daily and the phenobarbitone discontinued. She reported monthly for three months. Her weight had increased to 10 st. 10 lb. The thyroid gland was diffusely enlarged and there was marked exophthalmos. She still perspired profusely and the skin remained warm and moist. The pulse rate was 88 per minute and the pulse pressure was still increased. Her periods were irregular.

(7) A woman aged 46 had suffered from sweating, palpitation, nervousness and loss of weight for four months. Her periods were regular. On examination she had slight exophthalmos, a fine tremor of the hands, no enlargement of the thyroid and a soft warm moist skin. Her pulse was regular, rate 90 per minute, blood pressure 140/66. She weighed 9 stones. Thiouracil was administered 0.2 gm. t.i.d. for three weeks. She then weighed 9 st. 6 lb. The nervousness and other symptoms and signs were still present. The thiouracil was reduced to 0.1 gm. daily, and she was examined monthly for a further three months. Her weight had risen to 10 st. 6 lb. The thyroid gland was now enlarged, the skin was soft and moist and the tremor persisted. She had a very obvious unilateral exophthalmos. The pulse was still fast and the pulse pressure increased. Her periods were irregular.

(8) A woman, 44 years old, complained of nervousness, irritability, palpitation and sweating for six months. She also stated she had been losing weight. Her periods were regular. She weighed 9 st. 3 lb. and was a rather nervous, apprehensive patient. There was a fine tremor of the hands, a soft warm moist skin and no enlargement of the thyroid gland. The eyes were bright

and the conjunctivæ glistening. The pulse rate was 100 per minute and the blood pressure 140/60. A prescription for phenobarbitone grs.  $\frac{1}{2}$  b.i.d. and thiouracil 0.2 gm. t.i.d. was given and she was seen again in three weeks. Her weight was now 9 st. 11 lb. She was still nervous, had a tachycardia and an increased pulse pressure. The eyes were slightly prominent and the conjunctivæ moist and glistening. The thiouracil was reduced to 0.1 gm. daily and she reported monthly for four months. At the end of that time her weight had risen to 10 st. 10 lb., she sweated profusely and the palpitations persisted. There was diffuse enlargement of the thyroid gland, marked exophthalmos, tachycardia and an increased pulse pressure. Her periods were now irregular and she complained of hot flushes and giddiness.

(9) A woman aged 40 had suffered from sweating, nervousness, dyspnoea and loss of weight for six months. Her periods were regular. Her weight was 9 st. 5 lb. She had a warm, moist skin, a fine tremor of the hands and slight subconjunctival oedema. There was no enlargement of the thyroid gland. Her pulse rate was 90 per minute and the blood pressure was 145/70. She was given a prescription for phenobarbitone grs.  $\frac{1}{2}$  b.i.d. and thiouracil 0.2 gm. t.i.d. and was asked to report in three weeks. She then weighed 9 st. 11 lb. and still had tachycardia with an increased pulse pressure. The skin remained moist and warm, the tremor persisted and her eyes were very bright and glistening. The thiouracil was reduced to 0.1 gm. daily and she reported monthly for three months. Her weight at the end of that time was 11 st. 5 lb., she was very nervous, had definite exophthalmos, a fast pulse, a large pulse pressure and the thyroid gland was diffusely enlarged.

(10) A female patient, 45 years of age, complained of excessive sweating, lethargy and nervousness. Her periods were regular. There was slight exophthalmos on examination and her pulse rate was 95 per minute with a blood pressure of 150/75. Her skin was moist and warm. There was no enlargement of the thyroid gland but she had a fine tremor of the hands. Her weight was 9 st. 8 lb. Phenobarbitone grs.  $\frac{1}{2}$  b.i.d. and thiouracil 0.2 gm. t.i.d. were given and she was seen again after three weeks. Her weight had increased to 10 st. 2 lb. She stated she was still nervous. The exophthalmos was more marked. The sweating, tachycardia and tremor persisted. The thiouracil was continued for a further week and then reduced to 0.1 gm. daily. She reported monthly for three months. Her weight had increased to 11 st. 6 lb. The skin was warm but dry, the exophthalmos was very marked, the thyroid gland diffusely enlarged and the tremor and tachycardia with increased pulse pressure were still present.

## DISCUSSION

It is well known that there is usually some subjective improvement after about seven to ten days of thiouracil therapy. The patients feel less nervous and the sweating and flushing of the skin improve. None of the subjects in this series experienced any such symptomatic relief after a month nor even after three or four months. The effects of thiouracil, and indeed the clinical features of these cases demand further study.

*The Increase in Weight.*—An increase in the patients' weight is a most valuable indication of their response to thiouracil. Dunlop

has shown that this gain in weight amounts to over half a stone during the first month and to almost 20 lb. in a year. The average increase in weight of the patients in this series during the first three or four weeks was 7 lb., but after three to four months was 25 lb. This rather astounding increase in weight occurred while a maintenance dose of thiouracil was being taken, and was not associated with any other manifestation of improvement, the patients in some cases stating they felt worse.

*Exophthalmos.*—Dunlop stated that in his cases of thyrotoxicosis the associated exophthalmos usually persisted, although prolonged treatment with thiouracil resulted in the disappearance of the lid retraction in some. In this series of 10 cases 8 patients developed definite exophthalmos during the three to four months therapy with thiouracil and in the remaining 2 cases the eyes became slightly prominent.

*Enlargement of the Thyroid Gland.*—Thiouracil does not cause the thyroid gland to diminish in size although occasionally the gland becomes definitely smaller. In this series, 7 of the 10 patients showed progressive enlargement of the thyroid gland during the thiouracil therapy.

*Other Clinical Features.*—The diagnosis of hyperthyroidism in these cases had been based upon certain clinical features. All the patients were women, the average age being 42·5 years, the youngest 38 and the oldest 46. All complained of sweating, and 9 of loss of weight. Nervousness was a feature in 8 patients, dyspnœa in 4, palpitation in 6 and tiredness in 2. All the patients had a soft warm elastic skin with moist palms and a fine tremor of the hands. The eyes were either slightly prominent or unduly bright with glistening conjunctivæ in 9 of the cases. The average pulse rate was 99 per minute and the pulse pressure 76 mms. Hg.

The development of exophthalmos, the increase in size of the thyroid gland and the gross increase in weight of these patients, together with the persistence of their symptoms while on thiouracil therapy suggest that the original diagnosis of hyperthyroidism should be revised. The sex and age of the patients suggest that their symptoms may be associated with the menopause.

There are at least two pronounced changes in the hormonal pattern which develop at the menopause, an under secretion of œstrin and an over production of gonadotrophin. Zondek has shown that the gonadotrophic hormone not only continues to be formed after oophorectomy but is excreted in increased amounts. A change in the hormonal level of these patients may therefore have produced the clinical features which resembled so closely those of thyrotoxicosis. Albright demonstrated that hypo-œstrinism is not the direct cause of the vasomotor phenomena seen at the menopause because:—(a) following oophorectomy œstrin disappears long before the hot flushes begin; (b) during the menopause the œstrin level may be

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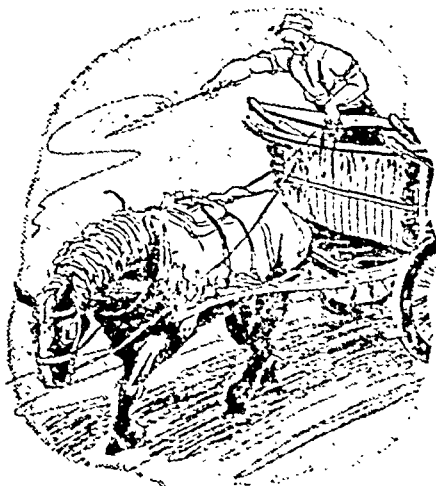
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brought above normal for a long time before the hot flushes cease ; (c) hypo-œstrinism due to pituitary disease is not accompanied by hot flushes. Œstrin therapy nevertheless relieves the vasomotor phenomena of the menopause after a considerable latent period. Treatment with œstrin also stops the over-production of gonadotrophic hormone after a similar latent period. Albright states that œstrin may exert its beneficial effect by decreasing gonadotrophic hormone production, but the evidence that the degree of flushing is proportional to the amount of gonadotrophic hormone produced is suggestive rather than conclusive. Kippin and Loeb have shown that removal of the gonads in female guinea-pigs leads to an increased production of gonadotrophic hormone and also of thyrotrophic hormone.

Exophthalmos developed in 8 of the 10 patients in this series during the period of observation. The relationship of the thyrotrophic hormone to exophthalmos has been the subject of much investigation. Friedgood in 1934 concluded that the exophthalmos which resulted from the administration of thyrotrophic hormone to animals was produced independently of the thyroid secretion and occurred more readily in an animal in a hypothyroid rather than a hyperthyroid state. Brain summarised the work of many investigators and stated that the exophthalmos of Grave's disease is almost certainly not primarily produced by thyroxine, but is the result of some other factor which may well prove to be the thyrotrophic hormone. Koutseff has described ocular changes in middle-aged women. He has designated these changes as the *occulo-palpebral syndrome* of the pre-menopausal period. This comprised palpebral œdema, œdema of the conjunctivæ, ocular hypertonia and perhaps transient myopia. These changes may well be caused by an increased production of thyrotrophic hormone at this time of life.

If Fig. A represents the normal relationship between the thyroid, pituitary and ovary then the changes that occur at the menopause may be represented in Fig. B. It can be seen that if thiouracil is given to women in the pre-menopausal state there will be interference with the synthesis of thyroxine and a further increased production of thyrotrophic hormone, Fig. C. Doby's has demonstrated that not only does thyrotrophic hormone produce an increase in the retro-orbital fat, causing the exophthalmos, but the fat content of other muscles in the body is increased, together with a generalised œdema of the cells in the fat depots.

It is feasible to suggest therefore that the symptoms of nervousness, sweating and palpitation seen in these patients together with the associated signs of tachycardia, increased pulse pressure, warm moist skin, œdema of the conjunctivæ and fine tremor of the hands are due to an increased activity of the anterior pituitary gland occurring in the pre-menopausal state in women who have been mildly hyperthyroid. Albright has suggested that increased secretion of the gonadotrophic hormone may cause the vasomotor phenomena while the mild

exophthalmos could be explained by associated excess of thyrotrophic hormone which would also stimulate the thyroid gland and thus give the other features of mild hyperthyroidism. The administration of thiouracil to these patients, by depressing the production of thyroxine, should increase the amount of thyrotrophic hormone and make their symptoms worse. This was so in every case. All the patients put on weight, probably due to the action of the thyrotrophic hormone

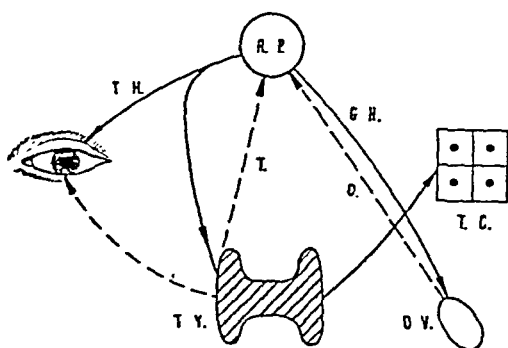


FIG. A.—Normal.

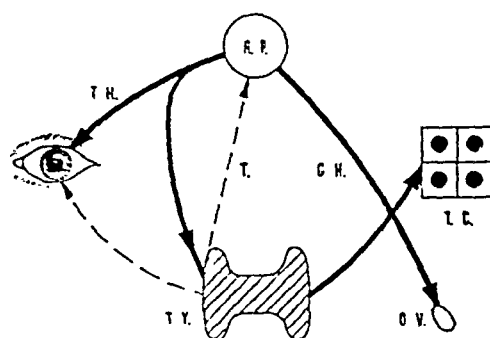


FIG. B.—Menopause.

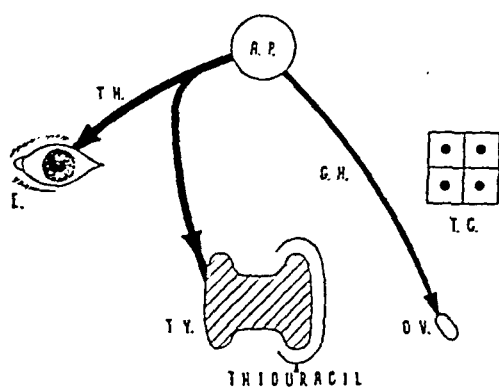


FIG. C.—Effect of Thiouracil.

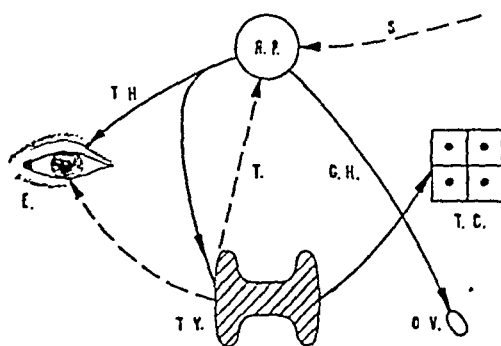


FIG. D.—Effect of Stilboestrol.

AP—anterior pituitary gland  
T—thyroid gland and thyroxine  
O—ovary and oestrin  
TC—tissue cells

TH—thyrotrophic hormone  
GH—gonadotrophic hormone  
—→—stimulation.  
---→—depression

increasing the fat content of the skeletal muscles, as shown by Dobyns. The thyroid increased in size in 7, and exophthalmos developed in 8 cases, while the nervousness and sweating persisted in all of them.

In all the cases the thiouracil therapy was discontinued after a time. Phenobarbitone was then given to five of the subjects. After eight weeks the enlarged thyroid gland, present in 3 of these cases, had decreased in size, the eyes were not so prominent although a degree of exophthalmos was still present in 4 of the five cases. Sweating and flushing persisted, however. The average loss of weight was 7 lb., the average pulse rate was 90 per minute and the pulse pressure 70 mms. Hg. at the end of this eight-week period.

To the other 5 patients phenobarbitone was also given, but in addition 5 mgms. of stilboestrol t.i.d. were prescribed. After two months of this therapy the thyroid gland, enlarged in 4 patients, had returned to its normal size. The exophthalmos, present in 4 cases, was greatly improved. The eyes were only slightly prominent in 2 patients and apart from an undue brightness were normal in the other 2. All these patients felt better, the sweating and nervousness were less, the average pulse rate was 82 per minute and the pulse pressure 55 mms. Hg. The average weight loss, however, only amounted to 9 lb. The effect of œstrin therapy may be represented diagrammatically in Fig. D.

It would thus appear that symptoms suggestive of thyrotoxicosis occurring in women at the time of the menopause are due to an over-activity of the anterior pituitary gland. Œstrin therapy should be given to such cases. If thiouracil is administered in full doses the symptoms become worse and the effects of excess thyrotrophic hormone soon become evident. Thiouracil, however, may be given for about fourteen days to control the effects of the excess thyroxine. It should then be followed by œstrin therapy.

#### SUMMARY

The effects of thiouracil upon menopausal women, having symptoms suggestive of hyperthyroidism, are described and the mechanism of production of these symptoms are discussed.

I wish to thank Professor Murray Lyon for the use of the case material and his help in the compilation of this paper.

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## THE EFFECT OF CHANGES OF TEMPERATURE ON THE HÆMOLYSIS OF ERYTHROCYTES

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IT has long been known that a fall in temperature increases the degree of hæmolysis in hypo-osmotic saline and in other hæmolysing solutions, while a rise in temperature has the opposite effect. The phenomenon has been studied in the range between 0° C. and 45° C.; beyond either extreme, rapid and complete hæmolysis occurs at all concentrations. Several theories have been put forward to explain this effect of change of temperature on osmotic hæmolysis, and none of them is made any simpler by the fact that our understanding of hæmolysis is very far from complete.

Jarisch (1921) attributed the effect of temperature changes to an alteration in the *pH* of the surrounding medium—an increase in hydroxyl ion concentration being produced at high temperatures and causing an increase in osmotic resistance, *i.e.* a decreased tendency to hæmolysis. Never regarded as an attractive theory, his results are greatly complicated by the use of buffers containing ammonium salts which are themselves hæmolytic. Jacobs and Parpart (1931), and Jacobs, Glassman and Parpart (1936) have correlated the change in osmotic resistance with a change in the base-binding capacity of hæmogoblin, both of which increase with rise in temperature, but it is difficult to visualise the base-binding capacity of a protein molecule inside an erythrocyte having an effect on the escape of that protein through the cell membrane. Ponder (1935) holds the view that the increased osmotic resistance at high temperatures is due to the escape of osmotically active substances from the cell interior. Lepeschkin (1935) attributes the change in osmotic resistance on cooling to mechanical damage to the cell membrane; at low temperatures, the cell is believed to be more prone to the injury produced by the swelling which occurs prior to hæmolysis.

The writer is of the opinion that the phenomenon can be explained in terms which are simpler than those and more in keeping with classical physical chemistry. As the name implies, osmotic hæmolysis depends, *inter alia*, on the osmotic pressure of the surrounding medium in which the cells are suspended. The osmotic pressure of any (hæmolysing) solution depends upon (1) the nature of the solute, (2) its concentration, and (3) the temperature. These factors are related in several equations, the best known of which is the van't Hoff equation;  $\Pi \times \Delta = n \times R \times T$ . Alteration in temperature, other things being equal, will have three distinct effects all of which influence the osmotic pressure. These are (*a*) a contraction of the volume on cooling with

a corresponding increase in the concentration. The reverse will occur on warming. (b) In the case of an electrolyte, the "degree of ionisation" alters with the temperature. Within the range  $0^{\circ}\text{C.}$  to  $37^{\circ}\text{C.}$ , the value of  $\Lambda/\Lambda_{\infty}$  (the "conductance ratio," which was formerly known as the "degree of ionisation") increases slightly as the temperature decreases. (c) The osmotic pressure is influenced itself, directly, by variations in the temperature according to the van't Hoff equation.

As the temperature falls, factors (a) and (b) will cause an increase in osmotic pressure while factor (c) will produce a decrease. It is now necessary to consider the magnitude of these changes.

(a) When 10.000 c.c. of distilled water at  $18^{\circ}\text{C.}$  is cooled to  $0^{\circ}\text{C.}$ , the volume of the liquid is reduced to 9.988 c.c.—a decrease of 0.012 c.c., or  $-0.1$  per cent. in volume, and there is therefore a corresponding increase of  $+0.1$  per cent. in concentration.

(b) At  $18^{\circ}\text{C.}$ , the value of  $\Lambda/\Lambda_{\infty}$  for M/20 sodium chloride is 0.879, and at  $0^{\circ}\text{C.}$  it rises to 0.888. These figures have been calculated from the data given for electrical conductivities in the *International Critical Tables* (1929). In the case of a uni-univalent electrolyte of the type NaCl, the van't Hoff equation  $\Pi \times \Lambda = (1 + \alpha) \times R \times T$ , where  $\alpha = \Lambda/\Lambda_{\infty}$  and from the above figures  $(1 + \alpha)$  becomes 1.879 at  $18^{\circ}\text{C.}$  and 1.888 at  $0^{\circ}\text{C.}$  This change in the value of  $(1 + \alpha)$  will make a difference of  $+0.5$  per cent. in the osmotic pressure in the above equation as the temperature falls from  $18^{\circ}\text{C.}$  to  $0^{\circ}\text{C.}$  This variable can be eliminated by the use of a suitable non-electrolyte, but the great majority of experiments in hæmolysis have been carried out in solutions of sodium chloride.

(c) In the calculation of the osmotic pressure, there are various equations in use. Fortunately, when dealing with dilute solutions of molarity of the order of M/20, it makes little difference whether one uses the original van't Hoff equation, the more elaborate Morse equation, or the ideal thermodynamic equation. Glasstone (1946, p. 671) gives the following figures for the osmotic pressure (in atmospheres) of a solution of sucrose at  $30^{\circ}\text{C.}$  containing 0.1 mole per 1000 gm. water:—

van't Hoff Equation.	Morse Equation.	Ideal Equation.	Observed Value.
2.40	2.47	2.44	2.47

For the sake of simplicity, the original van't Hoff equation has been used in all the following calculations.

A solution of sodium chloride in which the average blood hæmolyses to the extent of 50 per cent. contains 0.366 gm. NaCl per 100 c.c. (M/16.0) and has, according to the van't Hoff equation, an osmotic pressure of 2.795 atmos. at  $18^{\circ}\text{C.}$  and 2.622 at  $0^{\circ}\text{C.}$  (assuming the value of  $\alpha$  to be constant at 0.870, and ignoring the change in concentration due to the change in volume of the solution). This represents

a decrease of 0.173 atmos., equivalent to a change of  $-6.2$  per cent. in osmotic pressure as the temperature falls from  $18^{\circ}\text{C.}$  to  $0^{\circ}\text{C.}$

From a consideration of these figures, it is evident that factors (a) and (b) will produce a very small increase in the osmotic pressure, while factor (c) will produce a relatively large decrease; the net result will be a change of  $-5.6$  per cent.

At this point, it may be stated that the concept of a "degree of ionisation" has been considerably modified by the work of Debye and Huckel and more recently of Onsager, who have introduced and elaborated the theory of complete ionisation in which freedom of movement of the ions is to some extent impeded by their ionic atmospheres. The original "degree of ionisation" has been replaced by the activity coefficient ( $f_{\pm}$ ). In the following table the activity coefficients quoted are those given by Glasstone (p. 965); the values of  $\alpha$  have been calculated from the conductivity and freezing-point depression data set out in the *International Critical Tables*.

*Sodium Chloride Solutions at  $25^{\circ}\text{C.}$*

$m$	0.001	0.005	0.01	0.05	0.1	0.5
$f$	0.966	0.928	0.903	0.821	0.778	0.678
	0.979	0.953	0.935	0.876	0.841	0.736

The differences between  $f_{\pm}$  and  $\alpha$  are small and are significant, but provided that one adheres to one or the other, the errors introduced are not likely to affect the conclusions in any important detail. The original "degree of ionisation" has been used in all the following calculations.

When the temperature is increased from  $18^{\circ}\text{C.}$  to  $37^{\circ}\text{C.}$ , similar changes will occur, but in the opposite direction. The concentration will fall slightly due to an expansion of the hæmolysing solution; the degree of ionisation will decrease; and the osmotic pressure calculated by van't Hoff's equation will increase. As before, the change due to the third of these factors will outweigh those due to the first and second, and the net result will be an increase in osmotic pressure. For example, a solution of sodium chloride containing 0.366 gm. NaCl per 100 c.c. will have the following osmotic pressures (ignoring the expansion in volume and assuming  $\alpha$  to remain constant at 0.860): at  $18^{\circ}\text{C.}$ ,  $\Pi = 2.779$  atmos.; at  $37^{\circ}\text{C.}$ ,  $\Pi = 2.961$  atmos. The increase is 0.182 atmos. ( $+6.5$  per cent.).

In these circumstances, *i.e.* ignoring the changes in  $\alpha$  and in volume, the osmotic pressure will increase by  $0.173 + 0.182 = 0.355$  atmos. between  $0^{\circ}\text{C.}$  and  $37^{\circ}\text{C.}$  The average hæmolysis curve of normal, oxygenated, human blood at a dilution of 1:20 and at a temperature of  $19-21^{\circ}\text{C.}$ , is sigmoid in shape; 10 per cent. hæmolysis corresponds to a concentration of 0.395 gm. NaCl per 100 c.c., and 90 per cent. hæmolysis to a concentration of 0.332 gm. NaCl per 100 c.c. (Hendry, 1948). These concentrations are equivalent to

osmotic pressures of 3.04 and 2.55 atmos. respectively at 20° C. ( $\alpha = 0.870$ ). The difference (0.49 atmos.) is rather greater than the change in osmotic pressure which would be produced by altering the temperature from 0° C. to 37° C. (*i.e.* 0.355 atmos.). Hence the effect of such a change in temperature on the degree of hæmolysis at any specified concentration of sodium chloride will be considerable, and if it can be shown that the observed results are in quantitative agreement with the above discussion, it may be concluded with some confidence that the change in the degree of hæmolysis with alteration in temperature is a function of the accompanying change in the osmotic pressure of the hæmolysing solution.

Before proceeding to test this theory experimentally, two further complications have to be mentioned. The above arguments have dealt with alterations in the hæmolysing system, *e.g.* hypo-osmotic solutions of sodium chloride, to which the blood is added. Once the blood has been added to the salt solution, the erythrocytes are now suspended in a mixture of salt solution plus plasma. To this mixture is added the contents of any erythrocytes which may have hæmolysed should the salt solution have been sufficiently dilute. In the quantitative treatment of these complications, much depends on the ratio of blood to hæmolysing solution. It has been the writer's custom to use a final dilution of 1:20 because the volumes required are convenient to measure accurately, because this dilution of blood still leaves the mixture with a moderate degree of buffering power and control of the pH is essential, and because the amount of liberated hæmoglobin in 2.00 c.c. of the supernatant may be determined conveniently (Hendry, 1947). When normal human blood is used, the final mixture contains 9.50 c.c. of hæmolysing solution, 0.29 c.c. of plasma, and 0.21 c.c. of erythrocytes (the original blood having had a packed cell volume of 42 per cent.). The added plasma which is present does not alter the arguments presented above; its osmotic pressure and absolute volume will also vary with the temperature, and the ionisation of its electrolytes will depend on the temperature. As before, the changes in volume and in degree of ionisation will be small compared with the direct effect of temperature changes on the osmotic pressure.

Since normal human blood has been used in all experiments, the effect of the added plasma will be relatively constant; the volume of the added plasma is normally only about 1/35th of the total fluid present; but its osmotic pressure is higher than the osmotic pressure of solutions of sodium chloride which produce hæmolysis. The average freezing-point of serum ( $-0.56^{\circ}$  C.) indicates that it has an osmotic pressure at 0° C. which is the same as that of a solution of sodium chloride containing 0.942 gm. NaCl per 100 c.c. Assuming the degree of ionisation to be 0.870, this solution of sodium chloride has an osmotic pressure of 7.19 atmos. at 18° C., *i.e.* about 2.5 times the osmotic pressure of a solution of sodium chloride which will produce 50 per cent. hæmolysis.



Addition of 0.29 c.c. of plasma ( $\Pi = 7.19$  atmos. at  $18^\circ \text{C.}$ ) to 9.50 c.c. of a solution of sodium chloride containing 0.366 gm. NaCl per 100 c.c. ( $\Pi = 2.79$  atmos. at  $18^\circ \text{C.}$ ) will produce a final osmotic pressure of 2.92 atmos., neglecting for the moment the effects of the intracellular osmotically active material which will escape from the 50 per cent. of the cells which will have hæmolyzed. This increase in osmotic pressure due to the added plasma is significant, but small. More important is the fact that it is constant in experiments using normal human blood, and in those experiments in which a single sample of blood is used throughout the osmotic effects of the added plasma can be ignored. In experiments in which the blood of different individuals is compared its neglect will introduce an error, usually small, but depending on the variation in the packed cell volume of the different samples of blood. For the present purposes, it is sufficient to note that the added plasma is affected in the same way as the hæmolyzing solution as far as temperature changes are concerned.

The second complication arises from the increase in osmotic pressure of the hæmolyzing system due to the escape of osmotically active intracellular material during the course of hæmolysis. It has been assumed (although the assumption is not entirely valid) that nothing escapes from the cell until hæmolysis occurs, and that at the moment of hæmolysis, the cell liberates the whole of its contents. It will be obvious from the following calculations that the partial escape from the cell of any osmotically active material, will have only a vanishingly small effect on the total osmotic pressure of the surrounding medium even when working with a dilution as high as 1 : 20. The change in osmotic pressure due to this factor will be zero before hæmolysis begins, will increase in "sigmoid" fashion as hæmolysis proceeds, and will be maximal when hæmolysis is complete. The osmotic pressure inside the cell must be the same as the osmotic pressure of the surrounding fluid. Guest and Wing (1942) have shown that the erythrocyte behaves as a perfect osmometer until the point is reached when hæmolysis begins. Referring back to the arguments above, we may imagine that before hæmolysis starts, we have 0.21 c.c. of erythrocytes suspended in 9.79 c.c. of extracellular fluid (9.50 c.c. of hæmolyzing solution, plus 0.29 c.c. of plasma).

Since the normal hæmolysis curve is sigmoid in shape and approaches 0 and 100 per cent. hæmolysis asymptotically, it is quite impossible, by any method, to determine accurately the concentration of solute (or the osmotic pressure) at which hæmolysis "begins" or "ends." But the concentrations at which 10 and 90 per cent. of the erythrocytes have been hæmolyzed, can be determined with accuracy and between these limits, the hæmolysis curve approximates to a straight line.

At 10 per cent. hæmolysis (0.395 gm. NaCl per 100 c.c. ;  $\Pi = 3.02$  atmos. at  $18^\circ \text{C.}$ ) the osmotic pressure of the sodium chloride is reinforced by the addition of 0.29 c.c. of plasma ( $\Pi = 7.19$  atmos.)

and by 0.02 c.c. of intracellular material ( $\Pi = 7.19$  atmos.). It may be calculated that the addition of the plasma raises the osmotic pressure of the hæmolysing solution from 3.02 to 3.13 atmos. The addition of 0.02 c.c. of intracellular material raises it further to 3.15 atmos.

At 90 per cent. hæmolysis (0.332 gm. NaCl per 100 c.c.;  $\Pi = 2.54$  atmos. at  $18^{\circ}\text{C}$ .) the osmotic pressure of the sodium chloride solution is reinforced by the addition of 0.29 c.c. of plasma bringing it up to 2.63 atmos., and by 0.19 c.c. of intracellular material which raises the osmotic pressure to a final figure of 2.77 atmos. The liberated intracellular material thus contributes 0.02 atmos. at 10 per cent. hæmolysis, and 0.14 atmos. at 90 per cent. hæmolysis. These increases are very small and contribute approximately 0.015 atmos. for each 10 per cent. hæmolysis.

The position may therefore be summarised as follows. Five factors have been considered which will influence the osmotic pressure of a sodium chloride hæmolysing system. The first three are the results of changes of temperature; the last two are not. These factors are:—

(1) The effect of change of temperature on the volume and hence on the concentration of the hæmolysing solution. This effect is very small and has been ignored in the subsequent work.

(2) The effect of change of temperature on the degree of ionisation of sodium chloride. This effect is small provided that the change in temperature is small, but it has been allowed for in all calculations which follow.

(3) The direct effect of change of temperature on the osmotic pressure of the solution calculated by the van't Hoff equation. Quantitatively, this is the most important factor concerned.

(4) The increase in osmotic pressure of the hæmolysing solution due to the added plasma. This is also quantitatively important, but is constant in any experiment involving a single sample of blood. As all the following experiments are of this type, the effect of the added plasma has been ignored.

(5) The increase in osmotic pressure during hæmolysis due to the liberation of intracellular material. This effect is very small, and has also been ignored.

The theory is advanced that the change in the degree of hæmolysis produced by change in temperature is due to the effect of this change in temperature on the osmotic pressure of the hæmolysing solution. As the temperature falls, so the osmotic pressure decreases and the degree of hæmolysis increases. It remains to be shown that the theory can be verified quantitatively. Between 10 and 90 per cent. hæmolysis, the hæmolysis curve is steep and the difference between these two levels corresponds to a difference of only 0.48 atmos. at  $18^{\circ}\text{C}$ ., so that a very small change in osmotic pressure will bring about a relatively large change in the degree of hæmolysis. This state of affairs will

be most striking at the mid-point of the curve where a change of 0.005 atmos. pressure (*i.e.* about 1/500th of the total pressure) brought about by any means, will alter the degree of hæmolysis by about 1 per cent. Conversely, below 5 per cent. and above 95 per cent. hæmolysis, a comparatively large change in osmotic pressure will have a relatively small effect on the degree of hæmolysis, and these regions of the curve must be avoided.

### EXPERIMENTAL

*Methods, etc.*—In the following work, all experiments were carried out with blood obtained from normal healthy humans (blood donors). Coagulation was prevented by the use of heparin (one drop B.D.H. heparin dried off *in vacuo*). The blood was then fully oxygenated in a tonometer of 500 c.c. capacity; a constant slow stream of oxygen (previously bubbled through water) was passed into the tonometer which was rotated at frequent intervals. Complete oxygenation is most important. Its effect is to remove carbon dioxide from the blood (Hendry, 1947) and thus prevent changes in the *pH* of the blood while it is being handled. In all cases, the blood was diluted 1 : 20 in the hæmolysing solution. The percentage hæmolysis was determined by the method already described (Hendry, 1947).

The following values have been used for the degree of ionisation of sodium chloride at the temperature indicated :—

T (° C.)	5	10	15	20	25	30	35	40
$\alpha$	0.879	0.876	0.873	0.869	0.866	0.862	0.859	0.855

These figures were arrived at by extrapolation from values calculated from the data given in the *International Critical Tables* (1929) for electrical conductivities and freezing-point depressions. They correspond to solutions of concentration 0.366 gm. NaCl per 100 c.c. (M/16.0), which, in turn, corresponds to the solution which will produce 50 per cent. hæmolysis with the average specimen of blood.

Temperature control was effected by means of water-baths which kept to within 0.5° C. of the desired temperature. Osmotic pressures were calculated by the equation :—

$$\Pi = 0.01403 \times (1 + \alpha) \times T \times c$$

where *c* is the concentration of sodium chloride expressed in gm. of NaCl per 100 c.c. of solution.

*Hæmolysis at Constant Concentration.*—An idea of the magnitude of the change in the degree of hæmolysis at different temperatures is shown by the figures in Table I, where the blood was exposed to solutions of the same concentration of sodium chloride at different temperatures. The osmotic pressure at the corresponding temperature has also been included for comparison.

*Hæmolysis at Constant Osmotic Pressure.*—Using the equation given above, it is a simple matter to produce two solutions of sodium chloride of different concentration such that they will have the same osmotic pressure at two specified temperatures. A specimen of blood would then be expected to hæmolyse to the same extent in each solution at the corresponding temperature. As was anticipated, agreement is best towards the two ends of the hæmolysis curve.

TABLE I

*Hæmolysis at Constant Concentration.  
Time of Hæmolysis = 30 minutes*

<i>Blood BTSA—</i>			
Conc. NaCl (gm./100 c.c.)	0.350	0.350	0.350
Temperature (° C.)	4.0	18.0	35.0
$\pi$ (atmos.)	2.56	2.67	2.81
Percentage hæmolysis	94 per cent.	85 per cent.	36 per cent.
<i>Blood BTSE—</i>			
Conc. NaCl (gm./100 c.c.)	0.370	0.370	0.370
Temperature (° C.)	4.5	17.5	35.0
$\pi$ (atmos.)	2.71	2.82	2.97
Percentage hæmolysis	70 per cent.	50 per cent.	12 per cent.

TABLE II

*Hæmolysis at Constant Osmotic Pressure*

*Concentration of sodium chloride is expressed in gm. NaCl per 100 c.c. Osmotic pressure expressed in atmospheres. Time of hæmolysis = 30 minutes*

Blood.	Osmotic Pressure.	Temp. (° C.).	Conc. NaCl.	Percentage Hæmolysis.	Temp. (° C.).	Conc. NaCl.	Percentage Hæmolysis.
BTS 1	2.80	11.5	0.3740	8 per cent.	20.5	0.3638	7 per cent.
BTS 2	2.75	12.0	0.3666	12 "	22.0	0.3555	11 "
BTS 2	2.60	12.0	0.3466	55 "	22.0	0.3361	54 "
EBH	2.65	5.0	0.3616	10 "	20.5	0.3445	11 "
EBH	2.50	5.0	0.3412	51 "	21.0	0.3243	59 "
BTS 3	2.60	4.0	0.3561	57 "	16.0	0.3423	58 "
BTS 4	2.60	18.5	0.3402	45 "	34.0	0.3247	39 "
BTS 4	2.40	18.5	0.3140	89 "	34.0	0.2997	90 "
BTS 5	2.60	18.5	0.3402	58 "	34.0	0.3247	48 "
BTS 6	2.55	4.0	0.3492	39 "	35.0	0.3175	32 "
BTS 7	2.40	4.0	0.3287	41 "	35.0	0.2988	40 "
BTS 7	2.55	4.0	0.3492	11 "	35.0	0.3175	8 "

The average difference between the figures for the percentage hæmolysis in the two columns is 3 per cent. This figure is of doubtful mathematical interpretation, but at least it indicates that at constant osmotic pressure, blood hæmolyses always to the same extent irrespective of the temperature. There are numerous small technical difficulties. For example, after a mixture of blood and hæmolysing solution has been allowed to stand at 35° C. it begins to cool down as soon as it is removed from the incubator. As the temperature falls, the degree

of hæmolysis will increase. Thermostatically-controlled centrifuges were not available, and speed of manipulation therefore becomes a vital factor.

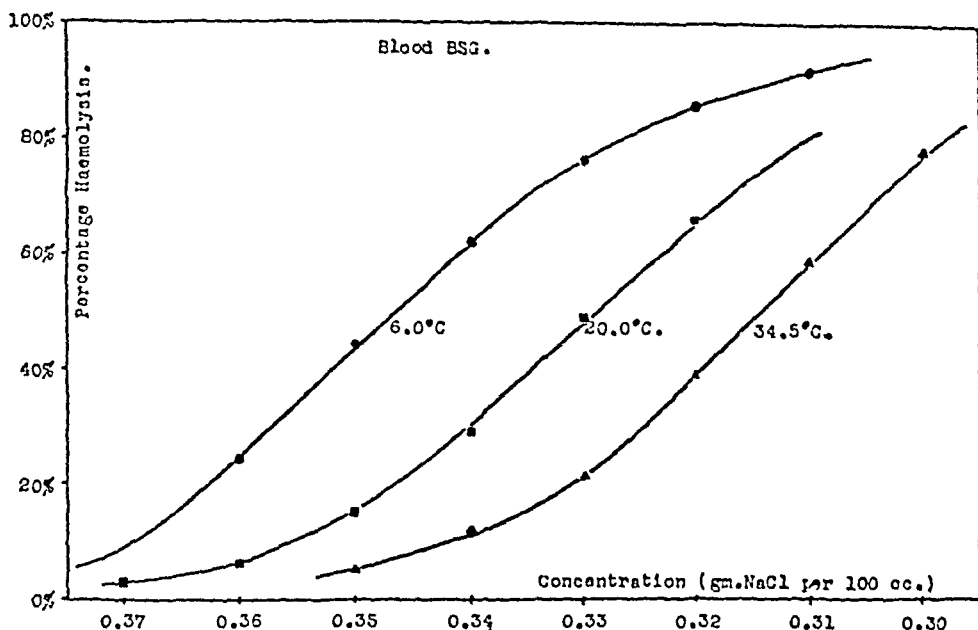


FIG. 1.—Hæmolysis curve of oxygenated blood. Dilution 1:20. Time of Hæmolysis, 30 minutes. Percentage hæmolysis plotted against concentration.

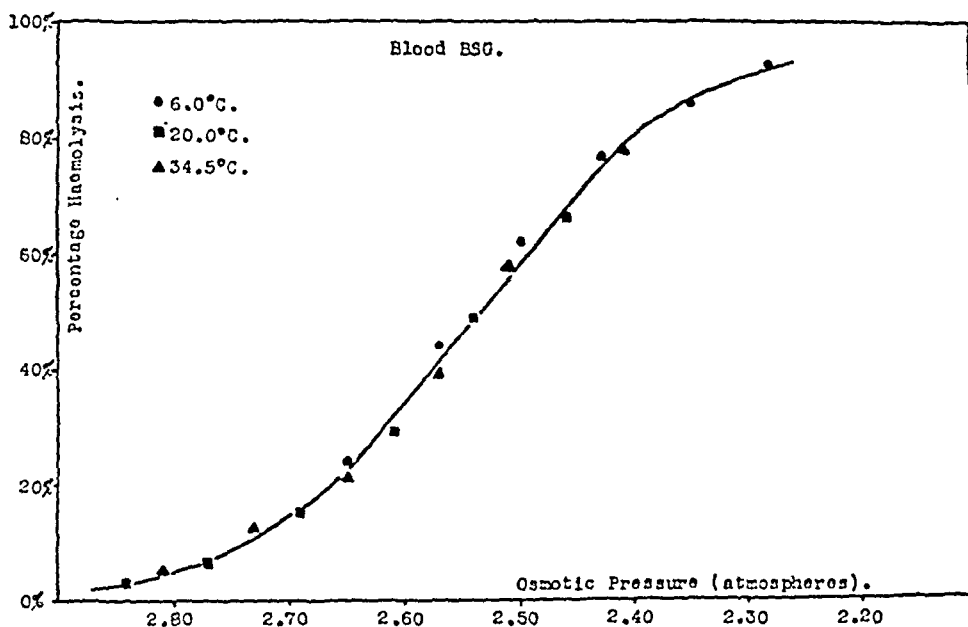


FIG. 2.—Legend as in Fig. 1, except that the percentage hæmolysis has been plotted against the calculated osmotic pressure.

The theory can be checked in an alternative way. Three series of solutions, each member differing in concentration by 0.010 gm. NaCl per 100 c.c., are equilibrated at three different temperatures. A single

specimen of fully oxygenated blood is distributed into each tube at a dilution of 1 : 20 and allowed to hæmolyse for thirty minutes. The tubes are then quickly centrifuged at high speed and the percentage hæmolysis determined in each.

When the percentage hæmolysis is plotted against the concentration in gm. NaCl per 100 c.c. (Fig. 1) three separate curves are obtained corresponding to the three selected temperatures. When the percentage hæmolysis is plotted against the calculated osmotic pressure in atmospheres (Fig. 2) all points lie on a single curve and the degree of hæmolysis is independent of the temperature.

### SUMMARY

The change in the degree of hæmolysis with change in temperature is due to the effect of the change in temperature on the osmotic pressure of the hæmolyzing system. Considered in relation to the osmotic pressure, the hæmolysis of erythrocytes is independent of the temperature within biological limits.

The author is greatly indebted to Dr R. A. Cumming and his colleagues in the S.E. Scotland Blood Transfusion Service who have supplied innumerable specimens of blood which have been used in this, and in previous experiments in hæmolysis. Part of the expenses of this research was defrayed by a grant from the Earl of Moray Fund of the University of Edinburgh to which the author is also indebted.

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## NOTES

At a Graduation Ceremonial held in the McEwan Hall on Wednesday, 20th July 1949, the following degrees were conferred :—  
**University of Edinburgh**

*The Degree of Doctor of Medicine*—Eric Gordon Barnes, England, M.B., CH.B., 1935 ; Albert Edward Claireaux, Scotland, M.B., CH.B., 1941 (*Commended for Thesis*) ; James Williamson Fraser, Scotland, M.B., CH.B., 1937 ; Alexander Duncan Gillanders, Scotland, M.B., CH.B. (with Honours), 1937 (*In absentia*) (*Highly Commended for Thesis*) ; David Gilmour, Scotland, M.B., CH.B., 1934 ; John Sharp Grant, Scotland, M.B., CH.B., 1934 ; Barnett Isaacson, South Africa, M.B., CH.B., 1921 (*In absentia*) ; Marjory Anne Keith, M.A., B.ED., Scotland, M.B., CH.B., 1944 (*Awarded Medal for Thesis*) ; Charles Knight McDonald, Scotland, M.B., CH.B., 1936 ; William Agnew Laws MacFadyen, Scotland, M.B., CH.B., 1936 ; Carmichael Mackie, Scotland, M.B., CH.B., 1930 ; Alan Bentley Monro, Scotland, M.B., CH.B., 1932 (*In absentia*) ; Mustafa Niazi, Egypt, M.B., CH.B., 1935 ; Alun Wynn Williams, Wales, M.B., CH.B., 1943 ; John Harley Young, Scotland, M.B., CH.B., 1927 (*Highland Commended for Thesis*).

*The Degree of Master of Surgery*—Andrew Wood Wilkinson, Scotland, M.B., CH.B., 1937 (*Awarded Medal for Thesis*).

*The Degree of Doctor of Philosophy*—Mohamed Mahfouz Abdel Aal, B.M., B.CH.(FOUAD) ; Barbara Heap Billing, B.A.(CANTAB.) ; Barbara Evelyn Clayton, M.B., CH.B. ; Helen Norman Duke, M.B., CH.B. ; Marion Huycke Ferguson, B.SC.(MANITOBA) ; Lynda Mary Halden Kerr, B.SC. ; John Alexander Loraine, M.B., CH.B., M.R.C.P.ED. ; Hugh Cyril William Stringer, M.B., CH.B.(N.Z.), M.R.C.P.E., D.T.M. AND H. (*In absentia*).

*The Degrees of Bachelor of Medicine and Bachelor of Surgery*—Mary Heather Aitken, Scotland ; John Allan Dalrymple Anderson, B.A.(OXON.), Scotland ; Oliver Archer, England ; Peter George Aungle, England (with Honours) ; Norren Edward Awunor-Renner, Sierre Leone ; James Stanislaus Barrett, Scotland ; John Allan Beattie, Scotland ; Michael Herbert Beaubrun, West Indies ; Boleslaw Bendkowski, Poland ; John Sanford Berkeley, England ; Leo Harry Berman, M.A., M.S.(COLUMBIA), U.S.A. ; William Findlay Blair, Scotland ; Dorothy Susanna Bleakley (*née* Macdonald), Scotland ; Halina Bobinska, Poland ; David Hugh Aird Boyd, Scotland ; James Denys Donald Brown, Scotland ; James Henderson Brown, Scotland ; John Bethune Brown, Scotland ; Thomas Airlie Brown, Scotland ; Ian Archer Cameron, Scotland ; Ian Henderson Cameron, Canada ; Margaret Middleton Cameron, Scotland ; John Hair Campbell, Scotland ; Maurice Alan Campbell, Scotland ; Andrew James Martin Carlin, Scotland ; Marion Lithgow Clark (*née* Robertson), Scotland ; Matilda Joanna Clerk, Gold Coast ; William Peter Cockshott, England ; Neil Conley, England ; John Cook, Scotland ; Walter Frederick Coulson, England (with Honours) ; Isobel Beatrice Craighead, Scotland ; Walter Allan Cranston, Scotland ; Janet Stella Darling, Scotland ; Robert Duncan McCallum Davie, Scotland ; Andrew Ross Dawson, Scotland ; Kenneth Steven Deas, Scotland ; Catriona Margaret Dempster, Scotland ; Pamela Mary Dodson, England ; Alice Beatrix Doherty (*née* Ritchie), Scotland ; Eleanor Janet Durrand, Scotland ; Frances

Muriel Falconer, Scotland; Helen Louise Amelia Prendergast Fermie, Scotland; Mary Caroline Riddock Fisher, Scotland; Hugh Munro Flett, Scotland; Mary Lee Fraser, Scotland; James Anthony Gordon Graham, Scotland; Peter Watson Grant, Scotland; George Husband Hardie, Scotland; Edgar Ross Harris, England; Muriel Grace Hartley, Scotland; Susan Elizabeth Herdman, Scotland; John Aitken Hislop, Scotland; Sheila Scott Hume, Scotland; Robert Stuart Malcolm Douglas Inch, Scotland; Thomas Theodore Scott Ingram, Scotland; James Jackson Ironside, England; Ailine Margaret Wallwyn James, England; David Andrew Johnson, Scotland; Ian Mackenzie Johnstone, England; Leon Kaufman, Scotland; Margaret Kennedy, B.Sc., Scotland; Iain Harrison Kidd, B.Sc., Scotland; Robert Kilpatrick, Scotland (with Honours); James David Edgar Knox, Scotland; Arnout Koch, Holland; Jurand Aleksander Krawiecki, Poland; Krechimir Krnjevitch, Yugoslavia; Janet Margaret Lamont, Scotland; John Alexander Hugh Lee, B.Sc., England; Anne Patricia Lerpinière, England; Isabel June Lim, Malaya; John Allon Liver, England; Malcolm David Webster Low, Scotland; Elizabeth Young McDonald, Scotland; Morag Stuart Macdonald, Scotland; Bevy Bruce MacKenzie (*née* Grenfell) England; William Alan Nelson Mackie, Scotland; Sheila Lochhead McKinlay, England; Iain Ferguson MacLaren, Scotland; Catherine Margaret Una Maclean, Scotland (with Honours); Donald Watt MacLean, Scotland; Edith Mary McLean, Scotland; James Douglas Farquhar McLean, Scotland; Kenneth Falconer Macrae MacLennan, Scotland; Thomas Jaffrey McNair, Scotland; Douglas Malcolm MacPhee, Canada; Donald Morrison McSwan, Scotland; Findlay Malcolm, Scotland; Annie Beaton Mann, Scotland (with Honours); Helen Frances Martin (*née* Steele), Ireland; George Henry Matheson, Scotland; John Hugh Michael Miller, B.A.(CANTAB.), England; John Lindsay Miller, Scotland; Victor Gordon Milne, Scotland; Charles John Morris-Mancor, Scotland; Winifred Alice Morton, Scotland; Helen Margaret Crawford Sutherland Mowat, Scotland; Catherine Russell Munnoch, Scotland; James Hood Neill, Scotland; John Ernest Newsam, England; Hartley Marshall Sutherland Noble, Scotland; Bernard Nolan, England; Samuel Emmanuel Nii-Amu Otoo, Gold Coast; John Andrew Owen, B.Sc., Scotland; Rosemary Elspeth Thurston Philp, Scotland; Hilary Ruth Pullon, England; Helen Maria Roberts (*née* Rebalska), Poland; Alexander Duff Robertson, Scotland; Elizabeth MacKay Ross, Scotland; Joan Mowbray Russell, Scotland; Helen Hay Scott, Scotland; Henry Gordon Seed, England; Robert Loudon Simpson, Scotland; Krystyna Maria Slawinska (*née* Andrzejowska), Poland; Lesley Dorothea Smith, B.Sc., Scotland; Jack Stewart Stark, Scotland; Thomas Stevens, Scotland; Sheila Margaret Stewart, Scotland; Ian Boyd Sutherland, England; Henry Bruce Torrance, Scotland; Dorothy Iona Troup, Scotland; Margaret Anne Tubbs, England; Gerald McDonald Ambrose Turner, England; William Bertram Vallance, Scotland; Ian Robert Verner, Scotland; Pearl Allan Walker, Scotland; Edith Jane Warner, Kenya; Phœbe Margaret White, Scotland; John McAllister Williams, England; Cedric William Malcolm Wilson, B.Sc., Scotland; David Ian Talbot Wilson, England; Janet White Worling, Scotland; Mary Elizabeth Shaw Wylie, Scotland; Gerard Young, Scotland; Robert Yule, Scotland (with Honours).

*Diploma in Public Health*—Robert Struan Fraser Adam, M.B., CH.B.; Eustace Akwei, M.B., CH.B.; Keith Hilliard Black, M.B., CH.B.(NEW ZEALAND)



(*In absentia*); Jean Arthur Gemmell, M.A., M.B., CH.B.; Derek William Horn, M.B., CH.B.; James Alexander Leitch, M.B., CH.B. (*In absentia*); John Patrick Sexton, M.B., CH.B.; Lotar Sheldon, M.D.(PRAGUE); Joseph Lee Watson, M.B., CH.B. (*In absentia*).

*Diploma in Industrial Health*—Walter Bolliger, M.B., B.S.(SYDNEY); William Henry Graham, M.B., CH.B. (*In absentia*); Ashit Kantha Niyogi, M.B.(CALCUTTA).

*Diploma in Tropical Medicine and Hygiene*—Mary Agnes Ashton, M.B., CH.B.; Mark Davey-Hayford, L.R.C.P.(ED.), L.R.C.S.(ED.), L.R.F.P. AND S. (GLASG.); Arthur Hugh Dunnett, M.B., CH.B.(ABERDEEN); Somesh Chandra Ghosh, M.B., B.S.(CALCUTTA); Patrick Murdoch Kirkwood, M.B., CH.B.; Syed Abdul Mannan, M.B., B.S.(OSMANIA), M.R.C.S.(ENG.), L.R.C.P.(LOND.); Robert Park, L.R.C.P.(LOND.), M.R.C.S.(ENG.); John Murray Ute Philip, M.B., CH.B.; Shih-Wen Wang, M.B., B.S.(MOUKDEN MEDICAL COLLEGE).

*Diploma in Medical Radiodiagnosis*—Agnes Murray Macgregor, M.B., CH.B.(GLASGOW); John Mackenzie, M.B., CH.B.; Charles Desmond Preston, M.B., CH.B.(ABERDEEN); David Forbes Ross, M.B., CH.B.(ABERDEEN).

*Diploma in Medical Radiotherapy*—Jeremiah Dermott Crowley, M.B., B.CH.(N.U. IRELAND); John Milligan, M.B., CH.B.

*Sister-Tutor Certificate*—Constance Jean Bell, John Christie, Fred Ellis, Isabella Cormack Hymers, Margaret Mary Kerr, Jane Anne Macdonald, Elizabeth Margaret Martin, Jeannie Margaret McLeod Martin, Grace Catherine Patrick, Janet Thomson Elliot Riddle, Kathleen Edna Robb, Margaret Elizabeth Ryder, Edith Mary Stephenson, Elizabeth Lewis Stevens, Ethel Mary Troughton, Marie Beatrice Nellie White, Katherine Emily Davie, Marion Campbell Loudon, Caroline Smith, Grace Hamilton Steel.

*The Polish School of Medicine at Edinburgh—The Degree of Doctor of Medicine*—Bronislaw Rozenblat, M.B., CH.B.(WILNO); Stefan Grzybowski, M.B., CH.B.; Jerzy Klimczynski, M.B., CH.B.

*The Degrees of Bachelor of Medicine and Bachelor of Surgery*—Jan Stanislaw Biskupski, Konstanty Maksimczyk, Alicja Lubicz-Sawicka, Aniela Szwede, Leon Buczek, Antoni Chrzaszcz, Cezary Cywinski, Jadwiga Dabrowska, Danuta Graczyk, Kazimierz Grochowalski, Krystyna Marja Kawa, Alina Klosowska, Gertruda Kolibabka, Robert Kowalewski, Tadeusz Krzyski, Wanda Kucharska, Kamila Marcinek-Balut, Michal Matuszewski-Topor, Ludwika Sawicka, Bronislaw Skibinski, Marja Starczewska, Jozef Franciszek Witek.

*Faculty of Medicine—The Cameron Prize in Practical Therapeutics*—Daniel Bovet, D.SC.(GENEVA). *Thesis Medallists*—Marjory Anne Keith, M.A., B.ED., M.D.; Andrew Wood Wilkinson, CH.M. *The Ettles Scholarship and Leslie Medal*—Peter George Aungle, M.B., CH.B.; Robert Kilpatrick, M.B., CH.B. (equal). *The Scottish Association for Medical Education of Women Prize*—Catherine Margaret Una Maclean, M.B., CH.B. *The Buchanan Scholarship in Obstetrics and Gynaecology*—Catherine Margaret Una Maclean, M.B., CH.B. *The Mouat Scholarship in the Practice of Physic*—Catherine Margaret Una Maclean, M.B., CH.B. *The Dorothy Gilfillan Memorial Prize*—Catherine Margaret Una Maclean, M.B., CH.B. *The James Scott Scholarship in Obstetrics and Gynaecology*—Annie Beaton Mann, M.B., CH.B. *The Murchison Memorial Scholarship in Clinical Medicine*—Cedric William Malcolm Wilson, B.SC., M.B., CH.B. *The Whaitt Research Scholarship*—Wiktor Tomaszewski, M.D., PH.D.(POSNAN). *The Gunning Victoria Jubilee*

*Prize in Physiology*—Ian Ferguson Sommerville, M.B., CH.B. PH.D. *The Gunning Victoria Jubilee Prize in Pathology*—Graham Malcolm Wilson, B.SC., M.B., CH.B. *The Beaney Prize in Anatomy and Surgery*—Robert Kilpatrick, M.B., CH.B. *The Keith Memorial Prize in Systematic Surgery*—Robert Kilpatrick, M.B., CH.B. *The Lawson Gifford Prize in Obstetrics and Gynaecology*—Robert Kilpatrick, M.B., CH.B. *The Singapore Medal*—Arnold Howard Banton, M.D. *The Annandale Medal in Clinical Surgery*—Margaret Kennedy, B.SC., M.B., CH.B. *The Murdoch Brown Medal in Clinical Medicine*—Gerard Young, M.B., CH.B. *The Ellis Prize in Physiology*—William Edward Balfour, B.SC.(LONDON). *The Wightman Prize in Clinical Medicine*—Cedric William Malcolm Wilson, B.SC., M.B., CH.B. *The Pattison Prize in Clinical Surgery*—John Reid Brown. *The Stirton Bursary*—David Nicol Sharp Kerr. *The Colonel Thomas Biggam Memorial Medal and Prize in Pathology*—Bruce Calder Paton. *The Lewis Cameron Undergraduate Prize in Bacteriology*—David Nicol Sharp Kerr, Donald McIntyre (equal). *The MacLagan Prize in Forensic Medicine*—Michael Robert King. *The Wellcome Medal and Prize in the History of Medicine*—Samuel Polsky, B.A.(PENNSYLVANIA), LL.B.(HARVARD). *The Cunningham Memorial Medal and Prize in Anatomy*—William Denney Smith. *The Senior John Aitken Carlyle Bursary in Anatomy and Physiology*—James Herkes Tait. *The Whiteside Bruce Bursary*—Lionel Gilbert. *The Ian Oswald Prizes in Anatomy*—William Harrison, James Kinneir Morrison, B.SC. *The Robert Wilson Memorial Prize in Chemistry*—Peter Harland Jaques. *The Vans Dunlop Prize in Physics and Chemistry*—Peter Harland Jaques. *The Vans Dunlop Prize in Botany and Zoology*—William Charles Constable. *The MacGillivray Prize in Zoology*—William Charles Constable.

The Address to the new Graduates was delivered by the Promotor, Professor Francis Albert Eley Crew, M.D., D.SC., PH.D., F.R.C.P.E., F.R.S.

At a meeting of the Royal College of Surgeons of Edinburgh held on 27th July 1949, Mr Frank E. Jardine, President, in the Chair, the following who passed the requisite examinations were admitted Fellows: Colin Ernest Lewer Allen, M.B., B.CH. UNIV. WITWATERSRAND 1940; Frederick Baar, M.D. UNIV. PRAGUE 1937, L.R.C.S. EDIN. 1947; Arnaud Jacques Biesman-Simons, M.B., CH.B. UNIV. CAPE TOWN 1937; Colin Sinclair Campbell, M.B., CH.B. UNIV. EDIN. 1939; Burjor Cavas Dastur, M.B., B.S. UNIV. BOMB. 1940; M.D. 1943, M.R.C.O.G. LOND. 1947; Patricia Reeves Davey, M.B., B.S. UNIV. SYDNEY 1938; Kenneth Drummond, M.B., CH.B. EDIN. 1944; John Milne Everett Jewers, M.B., CH.B. UNIV. ABERDEEN 1941; Donald Henderson King, M.B., B.S. LOND. 1942; George Lamb McEwan, M.B., CH.B. UNIV. ABERDEEN 1940; Ian Weir MacPhee, M.B., CH.B. UNIV. GLASGL. 1944; James John MacPherson, L.R.C.P. AND S. EDIN. (TRIPLE) 1943; Rameschandra Manjanath Nadkarni, M.B., B.S. UNIV. BOMB. 1931; MAHMOUD AHMED RADWAN, M.B., CH.B. UNIV. CAIRO 1930; Toleti Kanaka Raju, L.M.S. UNIV. MADRAS 1929, L.R.C.S. EDIN. 1948; Theodore John Reid, M.D. UNIV. FLORENCE 1934; Muhamed Hussein Saadi, M.B., B.S. ROYAL COLLEGE OF MEDICINE, IRAQ 1941, M.S. IRAQ 1946; Nagalingam Thirugnana Sampanthan, M.B., B.S. UNIV. CEYLON 1943; Humara Sayeed, M.B., B.S. UNIV. MADRAS 1942, M.R.C.O.G. LOND. 1948; Rabindra Narayan Sinha, M.B., B.S. UNIV. PATNA INDIA 1939; George Smith, M.B., CH.B. UNIV. ST ANDREWS 1942; Harold James Macklin

Stratton, M.R.C.S. ENG., L.R.C.P. LOND. 1940; Peter Alan Thorpe, M.B., CH.B. UNIV. LEEDS 1943; Herbert Spencer Trafford, M.B., CH.B. UNIV. MANCH. 1945; Harry Vincent Wingfield, M.R.C.S. ENG., L.R.C.P. LOND. 1943.

*Higher Dental Diplomates*.—The following candidates having passed the requisite examinations were admitted Higher Dental Diplomates: Charles Wilfred Bryant Coghlan, L.D.S., R.C.S. EDIN. 1942; Eric Siddons Foster, L.D.S. UNIV. SHEFFIELD 1942; Derek Leslie Goodridge, L.D.S., R.C.S. ENG. 1937; Alan Ferguson Hamilton, L.D.S., R.C.S. EDIN. 1941; Joseph Charles Basil Jones, L.D.S., R.C.S. ENG. 1931; John McDonald, L.D.S. UNIV. DURHAM 1940; William Donald MacLennan, L.D.S., R.C.S. EDIN. 1944; Herbert Guy Poyton, L.D.S., R.C.S. ENG. 1934; Ralph Beaumont Pickles, L.D.S. UNIV. BIRM. 1931; Alexander MacDonald Westwater, L.D.S., R.C.S. EDIN. 1947.

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh. The following passed the Final Examinations, and were granted the diploma of the L.R.C.P. EDIN., L.R.C.S. EDIN., L.R.F.P. AND S. GLASG.: Arthur Eliot Barr, Margaret Holden Batty, Constance Edith Belton, William Eric Bennie, Morris Cyril Berenbaum, Leo Harry Berman, David Graeme Brown, Edwin Louis Rees Brown, William Findlay Blair, Diana Pamela Mary Sylvester Cargill, Samuel Leo Chinchin, Leonard Isidore Davidson, Gulamhussein Mohamedali-Daya, James Devine, Daniel Joseph Docherty, Francis Doherty, Helen Erskine Ferguson, Leslie Montague Foegal, Vincent Gallone, Gordon Temple Wilson Gowdie, Joan Frances Greaves, Muriel Sheila Hill, David Donald Hillier, John Basil Matthew Hirst, Harold Jackson, James Jackson, Rex Gordon Jacomb, Ruth Winifred Joelson, Valerie Jones, Herbert Justitz, John David Keir, Rosemary Catherine Kennedy, Ryland Charles Lamberty, Veerapatheran Kishnasamy Moodaley, David Brierley Murray, Roger McNeill, Gibson Samuel Chieka Nzegwu, Rosemary Anne Page, Basil Raeburn, Gwyneth Richards, Helen Maria Roberts, Fritz Starer, Cornelius Stewart, Michael Stok, Christina Ellis Caldwell Taylor, Thomas Hamilton Walker, Brian Tennant Walters, Douglas Burns Stewart Watt, David Lloyd Williams.

## NEW BOOKS

*A.M.A. Interns' Manual*. Pp. 201. London: W. B. Saunders Company. 1948. Price 12s.

This small volume, written primarily for the young American graduate working in hospital, contains a wealth of factual information and useful practical hints arranged in a convenient form for quick reference. The material presented includes clinical and laboratory data, notes on drug administration, a list of useful preparations, and sections on toxicology, dietetics and physical medicine. Some pages are devoted to explanation of the laws and institutions relating to practice in U.S.A., but on the whole many young doctors in any country would be pleased to have this useful little book in their pocket.

*A Short Practice of Surgery.* By HAMILTON BAILEY, F.R.C.S., and R. J. MCNEILL LOVE, M.S. LOND., F.R.C.S. Parts II and III. London: H. K. Lewis & Co. Ltd. 1948. Price £2, 12s. 6d. the set.

This well-known book is being produced in five parts—a now familiar procedure necessitated by the shortage of block makers. It is designed to teach as much by diagrams and illustrations as by the written word. Much information can be assimilated by reading through its chapters, especially if the student is making a speedy revision before examination. However, most students will find that although almost every surgical subject is included, the information tends to be superficial and is not given in sufficient detail. As usual with these authors the illustrations are first class. A new chapter has been added in Part II on peptic ulcer.

*The Modern Management of Gastric and Duodenal Ulcer.* Edited by F. CROXON DELLER, M.D., M.R.C.P. Pp. 227, with 57 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 20s. net.

Dr Deller and his five contributors deserve the highest praise for successfully attempting the formidable task of adding to the literature on peptic ulcer.

The title is perhaps misleading in that at least half of the volume deals with problems of pathology and diagnosis. This, however, is far from a disadvantage since one has seldom read a more concise and unbiassed account of those fundamentals. The differential diagnosis of the common causes of dyspepsia is particularly well done.

In the chapters on treatment emphasis is put on the practical details rather than on seldom attained ideals. The sections on treatment of hæmatemesis and on the role of surgery are up to date and steer an admirable course amidst the rocks of controversy.

This book will have a wide appeal to general practitioners who wish to add to their knowledge of how to manage the difficult case of peptic ulcer.

## BOOKS RECEIVED

- By the Staff of the Mayo Clinic. Collected Papers of the Mayo Clinic and the Mayo Foundation. Volume 40, 1948.  
(W. B. Saunders Company, London) 55s.
- By Various Authors. Lehrbuch der Chirurgie. Band I.  
(Benno Schwabe & Co., Verlag, Basel) Fr. 74
- BERGIN, KENNETH G., M.A., M.D., D.P.H., A.F.R.A.E.S. Aviation Medicine, its Theory and Application. (John Wright & Sons Ltd., Bristol) 35s.
- BERNHEIM, BERTRAM M., M.D. The Story of the Johns Hopkins.  
(World's Work (1913) Ltd., Kingswood, Surrey) 12s. 6d. net.
- BLACK, NORMAN, L.D.S., R.C.S.ENG. Notes on the Theory of Dental Surgery.  
(Staples Press Ltd., London) 12s. 6d. net.
- BRASH, JAMES COUPER, M.C., M.A., M.D., F.R.C.S.ED., F.R.S.E. Cunningham's Manual of Practical Anatomy. Vol. II. Thorax and Abdomen. Eleventh Edition.  
(Oxford University Press, London) 21s. net.
- BROWNING, C. H., M.D., LL.D., D.P.H., F.R.S., and MACKIE, T. J., C.B.E., M.D., LL.D., D.P.H. Textbook of Bacteriology. Eleventh Edition of Muir and Ritchie's "Manual".  
(Oxford University Press, London) 50s. net.
- CARTER, C. W., M.A., B.M., B.Ch., and THOMPSON, R. H. S., M.A., B.Sc., D.M. Biochemistry in Relation to Medicine.  
(Longmans, Green & Co., London) 25s. net.
- CHAMBERLAIN, E. NOBLE, M.D., M.Sc., F.R.C.P. A Text-book of Medicine for Nurses. Fifth Edition.  
(Oxford University Press, London) 21s. net.
- DOGGART, JAMES HAMILTON, M.A., M.D.(CANTAB), F.R.C.S.(ENG.). Ophthalmic Medicine.  
(J. & A. Churchill Ltd., London) 32s. net.
- EVANS, C. LOVATT, D.Sc., F.R.C.P., F.R.S., LL.D.(BIRM.) Principles of Human Physiology (Starling). Tenth Edition.  
(J. & A. Churchill Ltd., London) 42s. net.

- EVANS, FRANKIS T., M.B., B.S., F.F.A.R.C.S., D.A. Modern Practice in Anæsthesia . . . . . (*Butterworths & Co. (Pub.) Ltd., London*) 50s. net.
- FOOTE, R. ROWDEN. Varicose Veins. . . . . (*Butterworths & Co. (Pub.) Ltd., London*) 32s. 6d. net.
- FULTON, JOHN F., O.B.E., M.D., D.S.C., LL.D.(BIRM.). Functional Localization in the Frontal Lobes and Cerebellum. . . . . (*Oxford University Press, London*) 15s. net.
- GOODALL-COPESTAKE, BEATRICE M. The Theory and Practice of Massage and Medical Gymnastics. Seventh Edition. . . . . (*H. K. Lewis & Co., London*) 21s. net.
- HARROWES, WILLIAM, M.D., M.R.C.P.E., D.P.M., F.R.S.E. Human Personality and its Minor Disorders . . . . . (*E. & S. Livingstone Ltd., Edinburgh*) 15s. net.
- HILL, H., F.R.SAN.I., F.S.I.A., A.M.I.S.E., and DODSWORTH, E., M.R.SAN.I., M.S.I.A. Sanitary Science Notes. Second Edition. . . . . (*H. K. Lewis & Co. Ltd., London*) 7s. 6d. net.
- HOSFORD, JOHN, M.S.LOND., F.R.C.S. Second Edition revised by COLTART, W. D., M.B., B.S.LOND., F.R.C.S. Fractures and Dislocations in General Practice . . . . . (*H. K. Lewis & Co., Ltd., London*) 21s. net.
- ISCHLONDSKY, N. E., M.D. Brain and Behaviour. . . . . (*Henry Kimpton, London*) 21s. net.
- KAMERBEEK, Dr A. ELISABETH H. M. Het Rubella-Probleem in Het Licht van Nederlandse Ervaringen. . . . . (*H. E. Stenfert Kroese's Uitgevers-Mij N. V., Leiden*) F. 7
- KAMERBEEK, Dr A. ELISABETH H. M. Het Rubella-Probleem in Het Licht van Nederlandse Ervaringen . . . . . (*Stenfert Kroese, Leiden*) 15s.
- KEMBLE, JAMES, CH.M., F.R.C.S.(ENG.), F.R.C.S.(EDIN.). Surgery for Nurses. . . . . (*John Wright & Sons Ltd., Bristol*) 21s.
- KIELY, PATRICK, B.S.C., M.D., M.CH.(N.U.I.), F.R.C.S.(ENG.). Text-book of Surgery. . . . . (*H. K. Lewis & Co. Ltd., London*) 45s. net.
- KRANTZ, JOHN C., Jr., and CARR, C. JELLEFF. The Pharmacologic Principles of Medical Practice . . . . . (*Bailliere, Tindall & Cox, London*) 55s. net.
- LICHTENSTEIN, BEN W., B.S., M.S., M.D. A Textbook of Neuropathology. . . . . (*W. B. Saunders Company, London*) 47s. 6d.
- O'RAHILLY, RONAN, M.B., M.S.C. Living Anatomy. . . . . (*Cork Univ. Press, Cork. B. H. Blackwell Ltd., Oxford*) 5s. net.
- PEPPER, O. H. PERRY, M.D. Medical Etymology. . . . . (*W. B. Saunders Company, London*) 27s. 6d.
- ROBINSON, JUDITH. Tom Cullen of Baltimore. . . . . (*Oxford University Press, London*) 21s. net.
- ROUTH, JOSEPH I., PH.D. Fundamentals of Inorganic, Organic and Biological Chemistry. Second Edition . . . . . (*W. B. Saunders Company, London*) 16s. 6d.
- ROUTH, JOSEPH I., PH.D. Laboratory Manual of Chemistry. Second Edition. . . . . (*W. B. Saunders Company, London*) 6s. 6d.
- ROWBOTHAM, G. F., B.S.C.(MANCH.), F.R.C.S.(ENG.). Acute Injuries of the Head. Third Edition . . . . . (*E. & S. Livingstone Ltd., Edinburgh*) 35s. net.
- SEWARD, CHARLES MACKAY, M.D., F.R.C.P.(EDIN.). Bedside Diagnosis. . . . . (*E. & S. Livingstone Ltd., Edinburgh*) 17s. 6d. net.
- Edited by STALLARD, H. B., M.B.E., M.A., M.D., F.R.C.S. Modern Practice in Ophthalmology, 1949 . . . . . (*Butterworth & Co. (Publishers) Ltd., London*) 65s. net.
- THOMPSON, LA VERNE RUTH, R.N., M.A., M.S. in Public Health. Introduction to Micro-Organisms. . . . . (*W. B. Saunders Company, London*) 21s.
- TIDY, SIR HENRY, K.B.E., M.A., M.D., F.R.C.P. A synopsis of Medicine? Ninth Edition . . . . . (*John Wright & Sons Ltd., Bristol*) 30s. net.
- TIDY, NOËL M., Member of the C.S.P., T.M.M.G. Massage and Remedial Exercises in Medical and Surgical Conditions. Eighth Edition. . . . . (*John Wright & Sons Ltd., Bristol*) 25s.
- WALSHE, F. M. R., M.D., D.S.C., F.R.S. Diseases of the Nervous System. Sixth Edition . . . . . (*E. & S. Livingstone Ltd., Edinburgh*) 17s. 6d. net.
- WEISS, EDWARD, M.D., and ENGLISH, O. SPURGEON, M.D. Psychosomatic Medicine. Second Edition . . . . . (*W. B. Saunders Company, London*) 47s. 6d.
- Edited by WHITE, CLIFFORD, COOK, FRANK, GILLIATT, SIR WM. Diseases of Women. Eighth Edition . . . . . (*Edward Arnold & Co., London*) 25s. net.
- WILLIAMS, HARLEY. The Healing Touch. . . . . (*Jonathan Cape, Thirty Bedford Sq., London*) 15s. net.
- WITTKOWER, ERIC, M.D. A Psychiatrist Looks at Tuberculosis. . . . . (*The Nat. Assoc. for the Prevention of Tuberculosis, London*) 12s. 6d.
- WOGLOM, WILLIAM H., M.D. Discoverers for Medicine. . . . . (*Oxford University Press, London*) 18s. net.

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# Edinburgh Medical Journal

*August 1949*

## INFLUENZA IN PERSPECTIVE

By C. H. ANDREWES, F.R.S., M.D., F.R.C.P.

INFLUENZA is the disease above all others in which a sense of historical perspective is needed. It is a disease which has periodically afflicted mankind with epidemics: the 1918-19 pandemic is the greatest plague ever known on this planet. In this age when infectious disease generally is apparently on the decline, we are apt to forget that that terrible scourge is only thirty years back in history. A geographical perspective is needed too: influenza pandemics can and do sweep all over the world; and, as we shall see, there is need to watch the whole world if we are to understand the meaning of the relatively minor doings of the influenza virus of nowadays.

Our historical and geographical enquiries meet with a difficulty at the outset. Influenza outbreaks are reported in the lay press from all sorts of countries, far and near, and we rarely have any certainty as to whether all the reports refer to a single disease. In probing the past our difficulty is still greater, for all the older information comes from an era in which the influenza viruses A and B were not known and hardly thought of. We must therefore begin our historical survey by contemplating the more solid ground of the present, about which we do know something.

We now know that from the jumble of undifferentiated upper respiratory infections it is possible to pick out a disease and call it influenza. By means of laboratory tests one can be certain that one is dealing with an entity—or rather two entities, for influenza may be caused by one or other of two antigenically unrelated viruses A and B. Of these, A causes by far the most trouble, at any rate in Britain. We may hope that in the course of years entities other than influenza will be picked out and made amenable to laboratory study: the most we can at present do with most of these others is to transmit them to human volunteers by means of filtrates.

I will tell you a little of what is known about Virus A, though much the same applied to B. It will produce an acute febrile upper respiratory infection in ferrets. I was fortunate in being associated with Wilson Smith and Laidlaw in the earliest work in this field; and the first virus to infect a ferret came from the garglings from my own throat. The disease is infectious from one ferret to another, so



that rigid isolation is necessary if the disease is studied in those animals. Fortunately the expensive and cumbersome method of study in ferrets has now been superseded by more convenient ones. Mice can also be infected; mice are cheap and easily handled in numbers. The disease produces in them a pneumonia rather than rhinitis, and the disease is not easily transmitted from mouse to mouse by contact. It is, however, difficult to infect mice directly from human material and we now have still better methods available involving the use of fertile hens' eggs.

Four main methods of infecting fertile eggs are in use—on to the chorio-allantoic membrane, into the amniotic cavity, the allantoic cavity, or the yolk sac. In studies of viruses each method has its own uses (Beveridge and Burnet 1946). For primary isolation of influenza virus from human material, amniotic inoculation is much the most sensitive method. Garglings need not be filtered: one does better by adding penicillin (with or without other agents) to suppress bacterial growth. But if you should ever try to isolate virus thus or send it to a laboratory, do please keep the material cold and see that it reaches the laboratory within an hour or two. Garglings sent through the post are often most unappetising by the time they reach their destination. The amniotic technique takes a little practice, but after one or two passes by this method, one can usually induce the virus to grow in the allantoic cavity. Allantoic inoculation is singularly easy, requiring little more than selection of a suitable spot on the egg surface through which to introduce a needle. Well-adapted viruses reach high titres in the allantoic fluid and this material is used as the source of virus for making formolised vaccines.

An important step forward was made when Hirst (1942) discovered that influenza virus in high concentration would agglutinate the red cells of fowls and other species. This finding is the basis of a quantitative test with which to estimate the amount of virus in a fluid. Further, the hæmagglutination is inhibited by appropriate antibodies; an A virus by an anti-A and B by anti-B, so that one has also a specific quantitative test for antibodies. All this to the virus worker is quite a luxury: he is used to laborious tests involving laboratory animals and taking days instead of hours to give an answer.

Hirst's hæmagglutination test has two practical applications. With it one can determine whether one has successfully isolated a virus in one's egg and if so which virus. The amniotic or allantoic fluid of the egg inoculated with human material is put up in dilutions in tubes against suspensions of washed red cells and agglutination looked for after an hour's standing on the bench. If it is positive and the presence of virus can be deduced, samples of the agglutinating fluid are mixed with anti-A, anti-B and control sera respectively, and a quick diagnosis is possible between A and B virus according to which serum inhibits the hæmagglutination.

There is an easier way to diagnose influenza than by isolating the

virus. Two samples of serum can be taken from a patient, the first "acute sample" within 3 days of onset of symptoms, the second "convalescent sample" taken at least 10 days from the onset. These are titrated by Hirst's method for the power to inhibit agglutination by A and B viruses. Human sera almost all contain some 'flu antibodies and in very varying amounts: hence the necessity for taking two samples, to detect an antibody rise in the course of the disease. If a fourfold or better rise in titre is found against A but not B, one can be fairly sure that the A-virus caused the patient's infection.

As an alternative to using this test, complement-fixation may be used, and this, though rather more troublesome to perform, contains rather fewer pitfalls for the inexperienced than the superficially simpler hæmagglutinin technique.

You may well ask: why bother about the differentiation of influenza from other infections? It does not affect treatment of the patient except in so far as it narrows the field when one is seeking the diagnosis of an unknown fever. The importance is, however, not for the individual patient but for helping our understanding of the disease. We need to know more of the spread, of the periodicity, of the clinical and epidemiological vagaries of influenza. All such studies mean a lot if one is sure what infectious agent is afoot; too many data from the past deal only with what was called influenza on clinical or epidemiological grounds. One example will suffice: much ink has been spilt in working out a periodicity for 'flu outbreaks. Recent work in America makes it probable that an apparently chaotic state of affairs is resolved once it is understood that two different viruses are causing epidemics: and if it is supposed that virus A caused, in the area concerned, an outbreak every two or three years, virus B having a periodicity of four to six years. Earlier workers not knowing about A and B would have had no chance of disentangling the puzzle. I have, I hope, made it clear that we can now recognise by antibody tests on sera and by recovering virus from garglings when influenza viruses A or B are active; we know roughly how they behave, nowadays. Let us now turn and look at the past, fully understanding that we shall have to guess what was influenza and what was not. We may nevertheless feel fairly sure that our guess will usually be right, even if we fail to separate A and B; for influenza is not as difficult to diagnose in the statistician's office as it is by the patient's bed.

There was quite a lot of influenza in Britain in the years up to 1847-48, when there was a big outbreak. After that, apart from a couple of minor flurries, the disease died down, not only in Britain but in Europe and North America, reaching a low ebb in the decade prior to 1889. There were, however, epidemics recorded in Russia in 1886 and 1887. These may be important, for the re-awakening of pandemic influenza seems to have started at Bokhara in Central Asia in May and June 1889. The disease spread thence to other parts of Russia and so to the rest of Europe and practically all over the world.

In many places the pandemic was seen in the form of a series of waves occurring in successive years. One can indeed hardly say how long the waves went on, for influenza has never fallen back to anywhere near the pre-1889 level. The incidence was highest in the earlier waves but the mortality higher in later ones: the disease remained true to its general traditions in killing chiefly the youngest and oldest age-groups (*cf.* Burnet and Clark, 1942).

Between 1892 and 1917 influenza settled gradually down to a level of activity rather lower and tending to fall, but, as I said before, appreciably higher than before 1889. There is a certain amount of controversy as to the beginnings of the terrible 1918-19 pandemic, since it arose out of more or less ordinary influenza, occurring particularly amongst the American expeditionary force in Europe. There were apparently spring epidemics of the ordinary type in army camps in the U.S.A. and in the ports in Europe to which they were sending troops. Particularly at Boston and Brest, a change in the character of the epidemic began about August. Mortality rose, with men dying acutely with the dreaded heliotrope cyanosis. In this second wave, of which the chief mortality was in October, the noteworthy character of the virus was its aptitude for killing, not as heretofore the very old and very young, but young adults. Later study revealed that this new and terrible property of the virus was already evident early in the pandemic, in June and July. The great lethal power for the 25-30 age group was more notable in the autumn wave; but the third wave, in 1919, showed a return towards normal age incidence, a tendency which continued in succeeding years. Before it was over the pandemic had spread all over the world and is estimated to have killed 15,000,000 people or more than were killed by military action in the first world war. Only the island of St Helena is believed to have escaped altogether. The tremendous effects of the pandemic were obscured at the time by the excitement due to the victory over Germany and her allies.

Bacteriologists working during this pandemic saw a varying picture. In many of them the colossal growth of Pfeiffer's bacillus in the lungs of fatal cases created an indelible impression—an impression so strong as to account for the hard dying of the theory that the Influenza bacillus (*Hæmophilus influenza*) causes influenza. For many years some maintained that others who could not find Pfeiffer's bacillus failed because of technical incompetence. It seems, however, true that some found Pfeiffer's bacillus dominant at one time and in one place and themselves failed, using the same technique, to find it at other times and places. In some areas staphylococci, pneumococci and streptococci caused more trouble than *Hæmophilus*. The *Hæmophilus* found were antigenically heterogeneous; they were more abundant late in the disease than at its onset. In dismissing them, as we safely may, as secondary or associated organisms, we must bear in mind Shope's findings (1931) in swine influenza. He found that the typical

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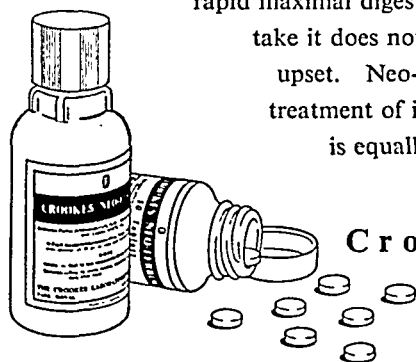
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picture of influenza in pigs in the American middle west was produced by a combination of the swine influenza virus and *Hæmophilus influenzae suis* (a virus and a bacillus closely related to their human counterparts). Virus alone caused almost nothing, bacillus nothing, the combination a severe fever, sometimes fatal. It is fair to say that observers of swine influenza in other parts of the world do not find that this association always occurs. Shope's findings do, however, suggest the possibility that some strains of virus may have a particular aptitude for synergic action with a particular bacterium.

#### INTERPRETATION OF THE PANDEMIC

It is unlikely that we can ever be certain now what caused the 1918 pandemic, though recovery of virus from another such pestilence might make us feel fairly sure. The chances seem, however, to be fairly great that the agent was a mutant or variant of influenza virus A—rather less probably B. It has been suggested that the lower mortality of the older age groups in 1918-19 was due to their past experience of the 1889-90 pandemic, but on the whole the evidence seems against that view. Was immunity produced by exposure to one wave of influenza in 1918 against the agent of a subsequent wave? We can answer this question with confidence: it sometimes was and sometimes wasn't. The facts suggest that a series of virus mutants appeared in 1918-19. Mutation is largely a matter of chance. If at the beginning of the pandemic an antigenically new mutant appeared, it would be able to spread and multiply abnormally thus directly favouring the statistical chances of the appearance of a second mutant. We may imagine that several strains of virus were circulating round the world and that this fact explains why, in different places, survivors of one 'flu experience might or might not be able to stand up against the next virus they met. Personally, I was lucky to suffer in the milder, July, wave in 1918. In November I was, as I now feel sure, gassed by the ward-room stove of the destroyer in which I was serving. Any ill person at that time had an automatic diagnosis of influenza, and I was sent into hospital at South Queensferry. I thus missed going out to help receive the surrender of the German fleet in the Firth of Forth, but I at any rate didn't catch 'flu from the other patients in the hospital. Burnet suggests that the reason for the great virulence of 1918-'flu was the increased speed with which it could spread all over the lungs before immunity could develop; also (rather less convincingly) that it is the very violence of reaction to the parasite of young adult tissues which was the cause of their undoing.

#### POST-1918 INFLUENZA

After 1890, the ripples caused by the pandemic disturbance gradually subsided, to use Greenwood's metaphor; so after 1919 influenza tended back to normal, and so too, as I have shown, did the age

incidence of deaths. Why is not this vicious virus with us now? or is it? The properties of a virus enabling it to spread and kill its millions are not necessarily those enabling it to live through hard times when most people are immune. Lack of ability to bridge the span from epidemic to epidemic may have led to dying out of the pandemic strain. The slow return of age incidence to normal suggests, however, the presence of the pandemic virus, at least in modified form, for some years. One occurrence suggests that it was in fact modified: New Caledonia and the New Hebrides in the Pacific escaped the pandemic in 1918-19, but influenza was introduced from Sydney in 1921. The morbidity was high, but mortality not apparently very high. The virus seems likely to have been at least related to the pandemic strain, for those on the island who had been elsewhere and had been through the pandemic were relatively immune.

### INFLUENZA SINCE 1933

The charts show the doings of influenza since 1920; the figures show the deaths in the 126 large towns in England and Wales (Figs. 1 and 2). It is evident that the main waves of A have come three or four years apart with a tendency for the successive waves to become smaller and more widely spread. Real epidemics cause a rise in deaths in the great towns to over the 1000 mark and rises to lower levels than that are always associated with activity of A-virus. B is apparently never so troublesome in this country.

The gradually lessening activity of influenza since 1919 may be a source of congratulation that after the defeat in this country of cholera, plague, typhoid, smallpox and more recently diphtheria, one more epidemic disease is on the wane. But let us not be too sure. Improvements in hygiene and in artificial immunisation have played an obvious part in the decline of the other diseases. But infectious diseases have a tendency to rise and fall irrespective of anything we may do: and influenza is one of these. We cannot possibly pretend that improved hygiene or preventive inoculation have played any part in the decrease of influenza. We should rather beware and remember that prior to 1889, and to a less extent prior to 1918, influenza seemed to be on the wane.

I have several times mentioned inoculation. The earlier vaccines we made from filtrates of infective mouse lungs gave rise to increased antibody on injection into man but were never proved to have prevented any influenza. They have been superseded by vaccines made from infected allantoic fluids of fertile eggs. The virus in these can be partly purified and concentrated either by adsorption on to and elution from fowl red cells or by cycles of centrifugation. It is inactivated by formaldehyde, gives good rises in antibody after one injection and will keep for some years in the cold. The most potent virus preparations cause rather too many local and general reactions and this forms

a limiting factor to the strength one can use. One can, however, get quite a good vaccine which will not cause too much trouble of that

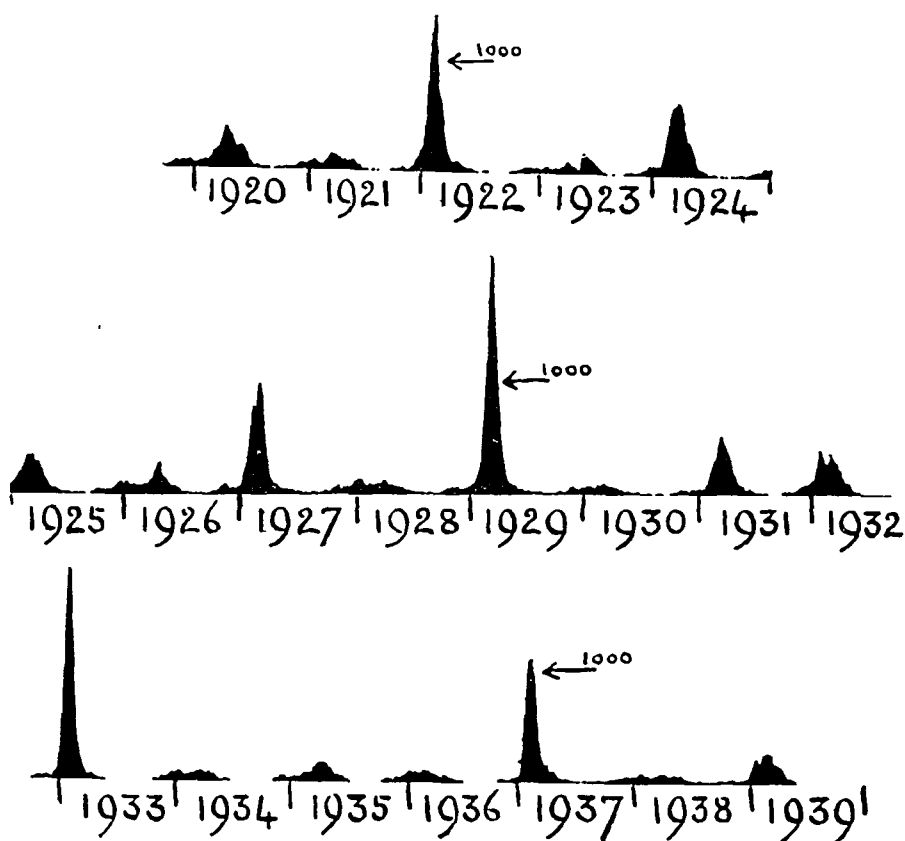


FIG. 1

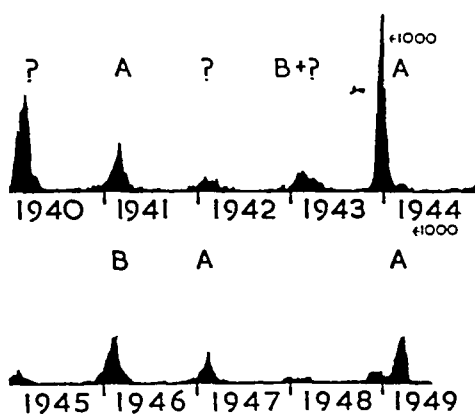


FIG. 2

kind. Now vaccines of this type gave in America in 1943 quite good results. In 5 of the 6 centres where they were tried, influenza in the vaccinated groups was only about a quarter of that in control groups.



That was in an A-outbreak. In a B-epidemic in 1946 protection was apparently even better, the reduction in 'flu incidence being about 10-fold respectively in two trials.

That, however, is not the end of the story. All observers are agreed that in 1947, both in America and Britain, a similar vaccine was a complete failure against the prevalent A-outbreak. There is also very good agreement as to the cause of that failure. The current virus, though undoubtedly A, was of an antigenic type rather remote from those known before, which had been used to make the vaccine. Here is the cause of all our recent worries. Within the group of A-viruses—and also amongst the Bs—are numerous serological strains sufficiently different from each other to upset the ideas of the epidemiologist and the hopes of the vaccinator. Now it is most interesting that the new type of A-virus—which has been called A-prime—turned up in 1946 in Australia and in 1947 in America, Britain, Sweden and Holland. In fact, since 1947 practically all A-viruses from all over the world, including a remote island in mid-Pacific, have been of the A-prime type. The serological types prevalent in the previous decade have taken quite a back place.

This apparent world-wide spread of strains made it urgent to study the epidemiology of influenza in a world-wide way. This was necessary not only for us to be able to understand better what is happening to influenza but also to enable us to be better prepared on another occasion with vaccine of a really appropriate composition. Army men are often said to be all set to fight a war with the weapons of the previous war: we do not want to be prepared only with the vaccine suitable for the previous epidemic. Accordingly, last year there was set up at Hampstead, as one of the activities of the World Health Organisation, a World Influenza Centre. Its functions are to collect information about the activity of influenza from all over the world and to collect strains of virus from all over the world, so that these can be typed serologically. Do not suppose that this typing is as simple as typing pneumococci or Salmonellas: the various 'flu strains cannot as yet be fitted into a small number of defined types; they seem rather to be labile creatures with a number of types shading into each other. The World Influenza Centre has made its contacts with laboratories in most European countries and with small numbers elsewhere; it has had visiting workers from a number of these to be trained in influenza techniques.

Last winter it had its first chance of going into action, and important results were obtained (Fig. 3). There has been dispute in the past: some hold that endemic influenza which is present all the time is successively activated in various countries in certain circumstances, giving an appearance of actual spread of an infectious agent; and others think that such spread is genuine. Last winter's happenings made it pretty certain that the latter is the case (Andrewes, 1949). The epidemic apparently began in Northern Sardinia in late September and

October 1948; it was noted soon after in Sicily and Calabria and soon spread all over Continental Italy into Switzerland, Austria, Southern France, probably into Northern Spain, into Western Germany, through Belgium into Holland and so to Britain, Denmark and Iceland. The incidence in Britain and Scandinavia was much lower than in Italy, France and Holland. We believe that a real spread occurred because strains sent to us from Italy, France, Switzerland, Holland, Britain and Iceland were serologically identical. They were of the A-prime group which turned up in 1947 but by refined serological methods could be

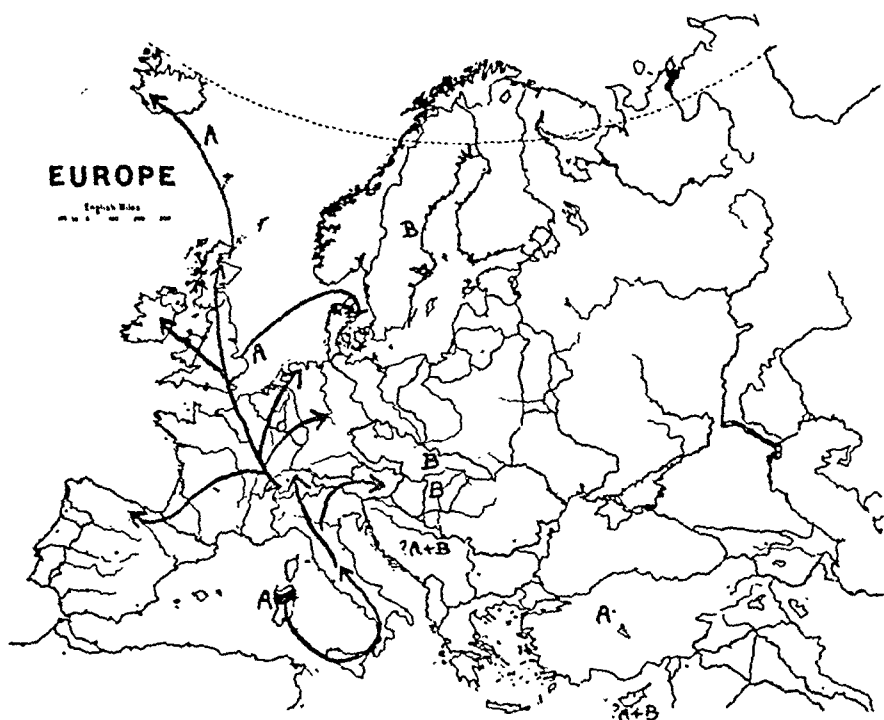


FIG. 3

identified as just perceptibly different from the 1947 strains while quite homogeneous among themselves. Besides this particular strain there were recognised minor activities of influenza B in Italy, Britain, Denmark, Sweden, Czechoslovakia and Hungary. There was an epidemic in Yugoslavia which may not have been true influenza at all and there was also an A-epidemic in Turkey; again we are not certain if the Turkish A-strain was related to those from Western Europe.

Why and how did this A-epidemic arise in Northern Sardinia? Magrassi reports that it began simultaneously in a number of villages and even attacked at the same time shepherds living in isolation. This supports other evidence which suggests that influenza epidemics do not arise entirely from a few obvious cases which then produce more disease by infecting others. It seems likely that sub-clinical infections

go on below the surface; possibly the virulence of the virus builds up gradually and the virus is already widespread before the epidemic is apparent. Thus the two theories of the spread of an epidemic may not be in real contradiction. Virus may really spread from one country to another; at the same time it may do so as a beneath-the-surface epidemic which only later breaks the surface and becomes obvious to all.

The widespread occurrence of the A-prime strain in Australia, America and Europe in replacement of older strains makes me suspect that influenza is a disease caused by a very labile virus which is always prepared with something new and unexpected for us. We may hope to make a good vaccine against current strains but must be prepared for such vaccines to fail one day, when a new strain turns up as happened in 1947. What are the prospects that the virus will one day produce a new mutant or mutants of the 1918-kind. I feel that this is much likelier to arise if an unusually widespread epidemic of ordinary 'flu occurs. This again is likelier if a large community has no contact for a long period with strains brewing elsewhere in the world. Thus much of Continental Europe had probably no experience of the A-prime virus which went visiting from Australia to America, Britain and Sweden in 1947; that may be why Italy and France had much more extensive 'flu this last winter than we did. On the whole I feel that the best hope that we may escape a new pandemic is not because of work done in the clinic and the laboratory but in the changing pattern of civilisation. With better mingling of the peoples of the world particularly as a result of air transport, no parts may be sufficiently remote so that the people lose their herd-immunity to influenza. There is a lot for you to learn about different aspects of influenza: I have tried to-night only to convince you that one thing necessary in understanding it is a very broad sense of perspective.

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## THE FACTORS THAT COMMONLY WORRY THE PATIENT IN HOSPITAL

By RONALD H. GIRDWOOD, M.B., CH.B., F.R.C.P.ED., M.R.C.P.LOND.

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IT is a fortunate circumstance that those responsible for the planning of medical curricula are now fully aware of the fact that psychiatry should not be considered as a subject quite divorced from the routine practice of medicine, and that medical students are commonly trained to recognise that the patient is not just an example of some disease catalogued in the textbook, but is an otherwise normal individual who has been unfortunate enough to fall ill, and that the course of the illness is frequently modified by emotional factors.

It is true that in all hospital records there is an entry, usually a very brief one, which purports to give an account of the family history and social history of the patient. It is also the case, however, that it is not uncommon for the doctor to be unaware of the extent to which his patient is worrying about matters connected directly or indirectly with the illness. There are occasions when the patient is unwilling to talk about his worries to the doctor or nurse, but will unload his troubles to the visiting minister or the hospital chaplain. Here the fields of the hospital physician, the minister and the psychiatrist overlap.

In 1923, Professor Richard C. Cabot, realising that the professions of the minister and the doctor should not be completely divorced, gave an address at Harvard University entitled "A Plea for a Clinical Year for Theological Students." Following this address, there began a movement in the United States of America for the training of ministers and theological students in certain aspects of pastoral care. It would be a retrograde step if the minister were to attempt to supplant the psychiatrist in the handling of manifest psychiatric disease, but it is evident that the clergyman will benefit from having some knowledge of psychology, psychosomatic medicine, psychotherapy, mental hygiene, juvenile delinquency, counselling, spiritual resources of illness, and, if possible, the names and probable course of the common diseases. Such training is now given at certain centres in the United States under the direction of the Institute of Pastoral Care, at Boston.

One such training centre is located at the University Hospital, Ann Arbor, Michigan, and here it has been found helpful in assisting ministers in their approach to the patient to give them an outline of the problems which experience has shown to be the ones that commonly trouble the patient in hospital. Comparison of the histories taken

by the chaplain or the social worker in various hospitals with those taken by the doctors from the same patients has shown that it is not unusual for the physician to be unaware of certain facts which would be of help to him in understanding fully his patient's illness. We therefore feel that it may be of value to put forward the following summary of the factors which we, working in different countries and different fields, have jointly found to be those most commonly causing concern to the patient during his time in hospital. This list is developed from one used in the training of ministers in pastoral care at the University Hospital, Ann Arbor.

Such a summary may be of value to the medical student who, passing from the study of pathology to that of clinical medicine, is too apt to think of the person in hospital as a case rather than a patient. He sees this person as a living example of pulmonary tuberculosis as described in his pathology textbook, and misses the more important fact that he is in the presence of a tragedy—the tragedy of the breadwinner of a family unexpectedly having his life thrown out of gear, and grave difficulties thrown upon his dependants. This aspect of medicine is obvious to the family practitioner, but is less obvious to the hospital physician and surgeon, and it is important that the medical student should be familiar with it from the start. The research worker in medicine, too, is one who may tend to lose his sense of proportion and forget the matters that are likely to worry the patient. The following summary is therefore given in tabular form in the hope that it may be of some value in reminding the hospital doctor, especially the younger one, of the main things about which his patients tend to worry, and that it may perhaps be of some use in the teaching of medical students especially at the difficult period of transition from the pre-clinical to the clinical years.

#### FEELING OF STRANGENESS AND HELPLESSNESS

While many patients experience a feeling of great relief at being admitted to hospital, there are others who, especially in the first few days, find difficulty in adapting themselves to the new environment. The following are the main matters that we have found to be a cause of concern to the patient at this time.

Away from home, perhaps for the first time.

Confined to bed ; strange high bed ; surrounded by patients in other beds.

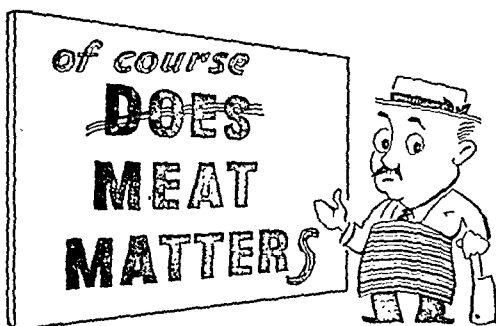
Clothes are taken away ; given strange, backward gown to wear.

Cannot come and go as one pleases.

Cannot select own food ; food is different and strange ; do not like this food, but don't like to say so.

Cannot take own bath ; must be bathed by a stranger when and how ordered. Sense of shame at being bathed by a nurse.

Cannot go to W.C. ; must use urinal and bedpan ; great difficulty in performing exhausting task of using bedpan.



You can hear how much it matters by listening in the shopping queues!

Well, everyone's working hard, and the harder people work the more they hanker after good satisfying meals. And "a good satisfying meal" to most people means a meat meal. Nothing else (they feel) can give the same fine sensation of well-being. Nothing else (they think) can keep them in hard-working trim.

Of course medical experience shows that this is only subjectively true—that although most people are accustomed to *enjoy* meat, and miss it when they can't get it, other foods can supply, and, in fact, do supply, the amino-acids in which meat's nutritional value lies.

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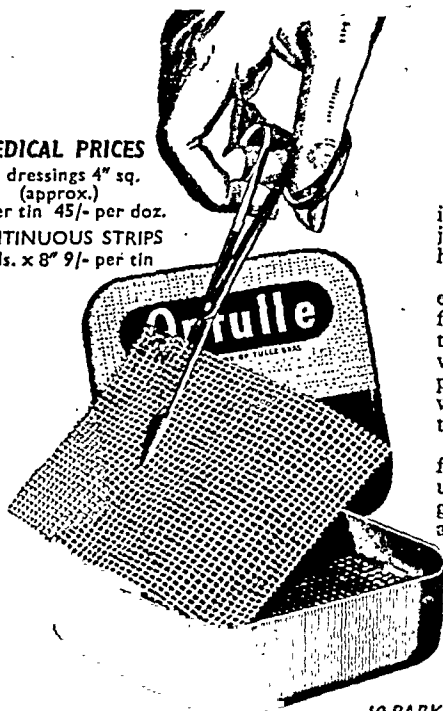
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Not in control of situation ; must submit to nurses, doctors, students, etc.

No privacy ; must submit to examination by any and all who desire.

Can't sleep for the noise of nurses working in the early hours of the morning.

The doctor in direct charge is too young, and the older ones are too busy to listen to my long story.

Can't tell the doctor all the facts, as it would embarrass me too much.

Life is made a misery by medical students using me as a guinea-pig for practising taking off blood, etc.

I'm not a person. I'm just another case.

### WORRY ABOUT RELATIVES AND DEPENDANTS

It is surprising how frequently the hospital patient worries a great deal about his family, often unnecessarily, without confiding this fact to the doctors or ward nursing staff. This is most commonly the case when the mother of a young family is hospitalised, and it is evident that such a patient must undergo severe emotional stress if she is apprehensive about the way in which her children are being cared for in her absence.

How will (wife, husband) get on without me ?

Who will take care of the children ?

Who will take my place in the family circle of activities ?

How can I keep the family from worrying about me ?

I am so lonely in this strange place !

### WORRY ABOUT JOB, EXAMINATIONS, ETC.

In many diseases, mental rest is perhaps the most important part of the treatment. The duodenal ulcer of the business executive is not likely to heal while he lies in bed fretting about the way in which his office is being run in his absence.

I am indispensable. The work cannot go on without me.

Supposing they find they *can* get on without me !

I cannot be idle like this, I must get out to-morrow.

I'm missing so many classes that I'll fail my examinations. I might even miss the examinations.

Supposing I have a deformity, or some weakness and have to change occupations.

It's all very well to tell me to take an open-air job, but what can I do ?

### FINANCIAL WORRIES

It is fortunate that in Britain the person who has the bad luck of falling ill does not have the further worry of how he is going to pay for his illness. Nevertheless, the patient may be very disturbed about financial matters in relation to himself or his family.



How will my family be supported while I'm in hospital ?  
 Supposing I become an invalid for life ?  
 While I'm here my business will be ruined, and so will I.  
 It's all very well to say to take a light job, but how can we live on the pay ?

#### CONCERN ABOUT THE ILLNESS ITSELF

It is natural that the patient should be very apprehensive about the nature and results of his illness. This is very often made worse by injudicious reading of home medical books or newspaper medical articles, and the patient may develop a state of extreme anxiety through misunderstanding such matter, or from overhearing injudicious remarks made near his bedside.

What is the nature, name, duration of this illness ? How long will I be in hospital ?

Will I have to have an operation ?

Will they tell me the truth ? Will they operate without warning me ? What are they hiding ?

Will it hurt ? How much ? Can I stand it ? Will I make a fool of myself ?

What about the anæsthetic ? I might say things I should not say.

Can I trust the doctor, the surgeon, the nurse ?

Why do they keep asking these foolish questions ?

Why do they keep taking my blood pressure, blood tests, etc. ?

Mrs Brown says her sister died of something just like I've got.

I saw my chart lying on the table. I've got a fatal disease.

I overheard the professor (doctor, sister, nurse, student, visiting doctor), saying I have cancer (six months to live, a hopeless outlook, came to hospital too late).

Is it hereditary ? Is it infectious ?

#### FEAR ABOUT THE DIAGNOSIS

Many patients have a fear of cancer, and many of those are afraid even to mention this to the doctor in case their fear should be realised.

Perhaps I have cancer (leukæmia, tuberculosis, syphilis), and they are hiding it from me.

I don't believe their diagnosis.

The doctor can find nothing organically wrong, and says it is imagination. But I still have the pain.

I don't want to see the psychiatrist. I'm not mad. Think of the disgrace.

I am a diagnostic problem. Nobody can find out what is wrong with me.

I can't tell them about the lump I feel in case it's cancer.

It's just like my father had, and he died of cancer.

## FEAR OF PAIN

It is surprising how much pain many patients can endure without complaint, but there is considerable individual variation in this respect.

Will it hurt? Will I be able to stand it?

I'd rather die than have another sternal puncture.

If only that other doctor would do it. He realises it can hurt, and does his best to make it painless.

Will I make a fool of myself, and show that I'm a coward?

Will I become a dope addict with all those drugs?

Will they give me something to make me sleep to-night?

## FEAR OF THE OPERATION

Possibility of dying on the operating table.

Fear of the anæsthetic; fear of talking, and revealing inner thoughts.

Fear of not getting sufficient anæsthetic, or of the operation being started too soon.

Difficulty of surrendering life into the hands of the surgeon and of God.

Is this operation necessary?

Fear of pain after the operation, evidence of this from seeing other patients after operation.

Modesty about being exposed during the operation.

## FEAR OF PHYSICAL HANDICAP OR DEFORMITY

Will my handicap or deformity spoil my appearance? Will people stare, pity?

Will my activities, job, sports be curtailed?

Will I become less attractive sexually? Incapable of sexual relations?

Will I lose my job? Have to change my occupation?

Will I be distasteful æsthetically? Repulsive to others?

Will I always have to have this colostomy?

## SENSE OF GUILT

A sense of guilt is not uncommon in association with illness, and may be revealed more readily to the minister than to the doctor or nurse.

Why did this happen to ME?

Am I being punished for some sin that I have committed?

Is it my fault? I did not take care of myself. I have waited too long.

Is it someone else's fault—my family, my doctor, my employer, my heredity?

Will they find out that I had V.D.? Think of the disgrace if my family find out.

I can't tell them how much alcohol I drink.

It must be because—review of all past sins, wickedness, disobediences, warnings, old wives' tales.

### FEAR OF GETTING WELL

This short summary is not intended to be an exhaustive treatise on the psychology or psychiatry of the hospital patient, but every physician is repeatedly faced with the patient who prefers to be in hospital.

Welcome haven and protection of hospital care.

Afraid of unpleasant environment of home, job, school, etc.

Love of attention received in hospital.

Compensation neurosis.

Need of an excuse for not succeeding in work, life, etc.

### FEAR OF DEATH

This matter is one that the patient usually discusses more readily with the minister.

Am I going to die? How long have I got to live?

Are they telling me the truth?

Am I ready to die? Why have I not led a better life?

What will happen if I die? To my family? To myself?

Will it be a long, lingering, painful death?

If I am to die, would it be wrong to take my own life to avoid misery?

Won't they give me something to put an end to it?

Can't they keep me going just a little longer in case some new cure is discovered?

I read in the Sunday newspaper about a cure for cancer. Why don't they get it for me?

In conclusion, we would make a plea for the abolition of the common practice of referring to any person in hospital, especially in that person's presence, as a "case." Most patients are not upset by this term, but its use is especially bad in the presence of medical students, who should be taught to regard the person in Bed 4 not as a "case of rheumatic fever," but as a patient who has been unfortunate enough to be afflicted with rheumatic fever. We would also like to stress the importance of co-operation and understanding between the doctor and the minister in relation to the patient.

### SUMMARY

An account is given of the main factors that serve as sources of worry to the patient in hospital.

## HÆMATOLOGICAL STANDARDS: EDINBURGH 1949

By EDWARD B. HENDRY, B.Sc., Ph.D., M.B., Ch.B.

*From the Clinical Laboratory, Royal Infirmary, Edinburgh*

THERE are so many methods of determining hæmoglobin, and so many ways of expressing the results, that confusion is inevitable. At least five methods are in common use either as standards of reference or as clinical procedures. These are (1) the oxygen capacity method, (2) the carbon monoxide method, (3) the total iron content, (4) the acid hæmatin, and (5) the alkaline hæmatin methods. All of these fall into one of two groups: (*a*) those which determine only the pigment which is capable of uniting with, and carrying, oxygen (*e.g.* the oxygen capacity method), and (*b*) those which determine the total pigment (*e.g.* the acid hæmatin method). The oxygen capacity method will not determine pigment in the form of methæmoglobin, sulphæmoglobin or carboxyhæmoglobin since these compounds do not combine with oxygen. For clinical purposes, determination of the *total* heme pigment is preferable since hæmoglobin derivatives such as carboxyhæmoglobin can be converted back again to physiologically active hæmoglobin in the body (given the opportunity), and methods measuring the total heme pigment are more generally useful. In practice, methods such as the oxygen capacity method require elaborate apparatus and a certain amount of manipulative skill; they are not, and never will be, "clinical" methods.

Results should be expressed in terms of grams of hæmoglobin per 100 c.c. of blood, but custom, and the calculation of various indices, have led to the continuing use of the method of expressing the concentration in terms of "percentage hæmoglobin." The standards corresponding to "100 per cent. hæmoglobin" vary from 13.8 (Haldane) to 17.3 (Sahli) grams of hæmoglobin per 100 c.c. so that, unless the standard corresponding to "100 per cent. hæmoglobin" is specifically stated, results expressed in terms of "percentage hæmoglobin" can be interpreted in very different ways. A hæmoglobin of 12.5 gm. per 100 c.c. corresponds to 91 per cent. (Haldane) or 72 per cent. (Sahli) with a variety of other possibilities in between. In some cases, the clinical hæmoglobinometer is stamped with the value to which "100 per cent. hæmoglobin" corresponds; in other cases it is not. The "normal" hæmoglobin concentration depends upon many factors, and involves the ever-recurring problem of defining what lies within the limits of "normal" and what does not. It is the custom in America and elsewhere to determine the average normal hæmoglobin concentration in each locality, and to take this value as the equivalent of "100 per cent. hæmoglobin" after suitable correction for variation in the red cell count. No recent determination of this value for the Edinburgh district seems to be available.

It is not the object of this paper to point out all the many sources of error in the colorimetric determination of hæmoglobin, but attention should be drawn to the difficulties of the visual matching of coloured solutions against a permanent colour standard. This technique, as a quantitative procedure, has been abandoned in all scientific work with the single exception of the determination of hæmoglobin. For all other procedures, it was replaced about thirty years ago by the introduction of colorimeters of the Dubosq type, and these in turn have been obsolete for at least ten years since the introduction of the photoelectric cell.

The acid hæmatin method of Sahli appears to be one of the most popular of the colorimetric methods. It should be stressed that it is quite useless when the total heme pigment is to be determined by photoelectric methods. The acid which is used precipitates out protein and lipoid giving an opalescent solution, and it may even precipitate the hæmatin itself, for this pigment is insoluble in acid solution. This opalescence, which increases gradually as the mixture of acid and blood is allowed to stand, constitutes one of the many difficulties in the visual matching of the brown colour. It completely invalidates photoelectric measurements, since the photoelectric colorimeter measures the total absorption of light, and it is immaterial whether this absorption of light be due to a coloured solution or to an opalescent one.

Undoubtedly the most satisfactory method for the determination of hæmoglobin is that of Clegg and King (1942) in which the blood is treated with strong alkali. The alkalinity keeps protein, lipoid and hæmatin in solution and the mixture is always optically clear. The photoelectric colorimeter is standardised by means of pure crystalline hæmin, and with moderately careful working the error in the determination of hæmoglobin can be reduced to the order of 1 in 200.

*Methods, etc.*—The original object of this work was to determine the important hæmatological standards for normal subjects living in this district. Blood was obtained from a series of normal, healthy adults attending the Edinburgh and S.E. Scotland Blood Transfusion Service. The subjects were not examined clinically, and the adjectives "normal" and "healthy" are used to denote that they felt sufficiently fit to volunteer to give a pint of their blood to the blood bank. Whether or not blood was actually taken depended on their passing a screening test in which blood from a finger-prick was examined by the method which employs solutions of copper sulphate of known specific gravity to exclude all potential donors with a hæmoglobin below a fixed level. It may be mentioned in passing that this method is slightly more unreliable than clinical inspection of the conjunctivæ or finger nails.

In practice, it was found that a few of the donors were either anæmic or were borderline cases, nevertheless they are included in the series since they constitute a part of the cross-section of the "normal, healthy"

population whose blood was under investigation. However, two of these donors were so grossly anæmic that they are placed in a separate section, but the selection of this little group is purely arbitrary for it is no easier to define what is "anæmic" than to define what is "normal."

The ages of the donors lay between 20 and 60. Old donors (*i.e.* those who have been previously bled) are not bled more than once in five months. The blood was taken off either in the afternoon (2 to 3 p.m.) or in the early evening (6 to 7 p.m.). The usual mixture of potassium and ammonium oxalates was used as anticoagulant. Withdrawal of a pint of blood takes less than ten minutes and the specimens were collected immediately afterwards, before the needle was withdrawn from the vein. It is safe to assume that no significant amount of hæmodilution occurs within this short time by withdrawal of extra-cellular tissue fluid into the vascular system.

Examination of the blood was started immediately after the specimen was obtained. Hæmoglobin was estimated by the method of Clegg and King (1942). Red cell counts were carried out in duplicate on two separate dilutions of each specimen, using standard diluting pipettes and a double-etched Bürker-Türk counting chamber. The average of all four determinations was taken. The packed cell volume was determined by centrifuging in a sealed hæmatocrit tube for 30-35 minutes at 3000 r.p.m. In the calculation of the percentage hæmoglobin, 14.8 gm. of hæmoglobin per 100 c.c. blood has been taken to represent 100 per cent. hæmoglobin throughout the following work.

## RESULTS

*First Series.*—This consisted of a series of hæmoglobin determinations carried out during 1946-49. The blood was taken for experiments on red cell fragility, and no hæmatological determinations other than the concentration of hæmoglobin was carried out. So random was the selection of these donors, that no record of the sexes was kept, but it may reasonably be assumed that they are approximately equally represented.

TABLE I

230 Donors (approximately 50 per cent.) male. Ages, 20-60.  
October 1946 to January 1949

	Mean.	S.D.	Coeff. of Variation.	Observed Range.
Hb. (gm. per 100 c.c.) .	14.4	1.55	10.8 per cent.	10.0-19.5
Percentage Hb. . .	97 per cent.	10.5	10.8 „	65-132

The large coefficient of variation is due to the fact that both sexes are represented in the table.

*Second Series.*—This consisted of a group of 50 males and a group of 50 females. All were old donors who had not been bled during the previous five months.

TABLE II  
*Old Blood Donors*

	Mean.	S.D.	Coeff. of Variation.	Observed Range.
50 Male Donors. Average age, 37. Feb./Mar. 1949				
Hb. (gm. per 100 c.c.) . . .	15.0	0.85	5.7 per cent.	13.1-16.8
Percentage Hb. . . . .	101.0	5.75	5.7 "	88-113
R.B.C. (millions) . . . .	4.96	0.32	6.4 "	4.25-5.72
Colour Index . . . . .	1.02	0.05	4.9 "	0.82-1.12
P.C.V. (percentage cells) . .	43.4	2.68	6.5 "	37.3-48.2
M.C.H.C. (per cent.) . . .	34.6	0.97	2.8 "	32.6-36.9
M.C.V. (cu. microns) . . .	87.6	3.16	3.6 "	74.3-94.8
50 Female Donors. Average age, 36. Feb./Mar. 1949				
Hb. (gm. per 100 c.c.) . . .	13.3	0.99	7.5 per cent.	11.2-15.4
Percentage Hb. . . . .	90.0	6.66	7.5 "	76-104
R.B.C. (millions) . . . .	4.61	0.28	6.1 "	4.03-5.32
Colour Index . . . . .	0.98	0.07	7.0 "	0.80-1.13
P.C.V. (percentage cells) . .	39.7	2.23	5.6 "	35.1-45.0
M.C.H.C. (per cent.) . . .	33.5	1.04	3.1 "	30.9-35.6
M.C.V. (cu. microns) . . .	86.2	5.37	6.2 "	74.4-97.8

*Third Series.*—In order to determine the effect of repeated blood withdrawals, another series of new blood donors who had not previously been bled, was examined.

TABLE III  
*New Blood Donors*

	Mean.	S.D.	Coeff. of Variation.	Observed Range.
30 Male Donors. Average age, 30. Mar./Apr. 1949				
Hb. (gm. per 100 c.c.) . . .	14.9	0.76	5.1 per cent.	13.1-16.0
Percentage Hb. . . . .	101.0	5.05	5.1 "	89-108
R.B.C. (millions) . . . .	5.00	0.32	6.4 "	4.12-5.73
Colour index . . . . .	1.01	0.05	5.0 "	0.90-1.09
P.C.V. (percentage cells) . .	43.7	1.78	4.1 "	40.2-47.5
M.C.H.C. (per cent.) . . .	34.0	0.96	2.8 "	32.6-36.4
M.C.V. (cu. microns) . . .	87.4	4.11	4.7 "	79.4-97.5
30 Female Donors. Average age, 34. Mar./Apr. 1949				
Hb. (gm. per 100 c.c.) . . .	13.4	1.12	8.4 "	11.0-16.3
Percentage Hb. . . . .	90.0	7.52	8.4 "	74-110
R.B.C. (millions) . . . .	4.51	0.33	7.3 "	3.98-5.15
Colour index . . . . .	1.00	0.06	6.0 "	0.82-1.11
P.C.V. (percentage cells) . .	39.4	2.84	7.2 "	32.1-47.2
M.C.H.C. (per cent.) . . .	33.8	1.06	3.1 "	30.3-35.9
M.C.V. (cu. microns) . . .	87.5	4.28	4.9 "	78.1-95.3

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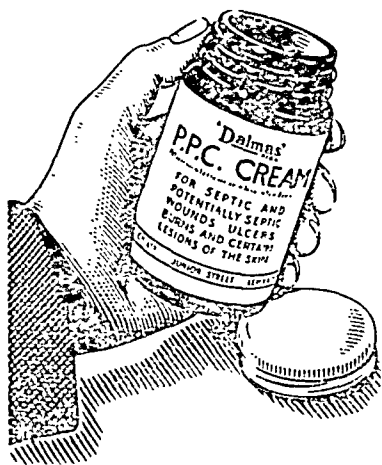
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It soon became obvious that there was going to be no significant difference between the second and the third series, and for that reason, the third series was confined to only sixty cases.

The difference in percentage hæmoglobin (Table II) between the two sexes is statistically significant. The standard error of the difference between the two means is 1.99, and the difference between the two means (11 per cent. Hb.) is 5.5 times this standard error. The conventional level of difference is usually taken as twice or three times the standard error.

The average percentage hæmoglobin in all cases recorded in Tables II and III is 96 per cent. which agrees very well with the average figure in the first series of unselected cases (97 per cent.). Blood which is used for transfusion in this district will probably therefore have a hæmoglobin concentration in the neighbourhood of 96-97 per cent.

If twice the standard deviation is taken as the normal limit of variation, there is the strong probability that any male with a hæmoglobin of less than 90 per cent., or any female with a hæmoglobin of less than 76 per cent., is pathologically anæmic, and this constitutes an approximate definition of the word "anæmic." But it must be remembered that the limit of 2 S.D. covers only 95 per cent. of normals. The writer's own hæmoglobin has varied between 119-120 per cent. for several years and this is just outside the limit of the mean + 3 S.D. for males.

There are a number of people, otherwise normal, who have a hæmoglobin at, or near, the lower limit of normality. A very short series of these cases has been collected. The first case was rejected from Table II, the second from Table III. The others have been collected subsequently and in all they represent 11 cases out of 450 blood donors.

#### *Fourth Series.—*

Sex.	Age.	Per cent. Hb.	R.B.C.	P.C.V.	
M.	35	63	5.03	32.5	Slight fatigue only.
M.	48	66	4.77	36.1	No symptoms. Partial gastrectomy eleven years ago.
M.	45	53	4.74	30.9	No symptoms. Gross dietary deficiency. Cured by iron.
F.	28	74	4.18	35.1	No symptoms.
M.	45	72	4.51	36.9	No symptoms.
F.	25	64	4.17	31.1	Breathlessness; cystitis.
M.	54	79	5.13	38.4	No symptoms.
F.	20	76	4.63	34.2	Rectal hæmorrhage two weeks ago.
F.	25	72	4.75	34.7	No symptoms.
F.	32	76	4.54	35.5	No symptoms.
F.	21	73	5.76	...	No symptoms. Cured by iron.

These cases were referred to their family doctors and with two exceptions, were lost sight of. Cases of this type do not come under medical supervision and a more extensive study of them might be worth while.

*The Hæmoglobin Coefficient.*—In order to make allowance for the effect of variation in the red cell count on the hæmoglobin concentration, Osgood introduced the "hæmoglobin coefficient" which is defined as the concentration of hæmoglobin corrected to a standard red cell count of 5.00 million. This coefficient is taken as the correct value to which "100 per cent. hæmoglobin" corresponds, and theoretically, it should be independent of the sex. In the 160 cases recorded in Tables II and III the hæmoglobin coefficient is as follows:—

TABLE IV  
*The Hæmoglobin Coefficient*

	Mean.	S.D.
80 Male Donors . . .	15.06	0.75
80 Female Donors . . .	14.58	1.00
Mean . . .	14.82	

The standard error of the difference between the means for the two sexes is 0.14, and the difference between the two means (0.48) is 3.4 times this difference. The difference in hæmoglobin coefficient between the two sexes is therefore probably significant. However, in order to avoid the extra complication of having a different coefficient for each sex, it is simpler, and introduces little error to take 14.8 gm. Hb. per 100 c.c. as being equivalent to "100 per cent. hæmoglobin" for both sexes.

#### SUMMARY

The hæmoglobin concentration, red cell count, packed cell volume, and derived indices are given for a series of 80 normal males and 80 normal females. The figures have been analysed statistically.

The hæmoglobin coefficient for normal adults in this district is 14.8 Hb. per 100 c.c. of blood. This figure should be taken to represent "100 per cent. hæmoglobin."

There is a strong probability that, on this standard, any male with a hæmoglobin below 90 per cent., or any female with a hæmoglobin below 76 per cent. is pathologically "anæmic." A short series of 11 such cases is described and it is interesting to note that 5 of these are males. All 11 felt sufficiently well to volunteer as blood donors.

The author is again indebted to Dr R. A. Cumming and his colleagues of the Edinburgh and S.E. Scotland Blood Transfusion Service for all the specimens of blood which were required for this investigation.

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## PNEUMOCOCCAL INFECTIONS

By J. T. SMEALL, M.C., M.B., Ch.B., D.P.H.

Formerly of the Bacteriology Department, Royal Infirmary, Edinburgh

ROUTINE typing of pneumococci was carried out in this laboratory from 1931 to 1945. The first stimulus came when Edinburgh was one of the centres selected by the Therapeutic Trials Committee of the Medical Research Council to study the effect of Type I and Type II antisera on the corresponding type of pneumonia. Serum therapy in the treatment of pneumonia had been adumbrated as long ago as 1891 by the Brothers Klemperer and Emmerich and Fowitzky, but it was only in the 1920's that any serious attempt had been made to evaluate this method. So far some improvement had been reported in Type I cases and doubtful reactions with Type II.

It was thus our first duty to let the clinicians know as soon as possible if Types I or II pneumococci were responsible for the pneumonia cases under their care. The result of this trial has been reported elsewhere and requires no further reference here.

Up till now, typing had depended on the intraperitoneal inoculation of a mouse with a subsequent agglutination test on the peritoneal exudate. At this point, however, our interest received a further stimulus when, in 1932, Armstrong, simultaneously with Logan and Smeall (of this department) pointed out that pneumonic sputum could in many cases be typed directly by the admixture of sputum and anti-serum. An homologous serum caused the pneumococci to show a characteristic swelling of the capsule, which was readily recognisable by the "seeing-eye." This reaction had been reported by Neufeld in 1902, but it had not been made use of until Armstrong employed it on the peritoneal exudate of the inoculated mouse in preference to the usual agglutination test.

In order to test the value of this "Direct Test," as a quick method of diagnosis, each pneumonic sputum was submitted to a three-fold test, viz. :—(1) Direct test. (2) Culture on blood agar plate. (3) Intraperitoneal inoculation of a mouse. Using Types I, II and III antisera, the only sera available at that time, a substantial number of cases was gradually accumulated. Briefly the results were as follows :—

Type I pneumonia	.	.	155 cases—78·7 per cent. correctly diagnosed by the				
							" Direct Test "
Type II pneumonia	.	.	320 " —89·7	"	"	"	"
Type III pneumonia	.	.	79 " —57·0	"	"	"	"
Group IV pneumonias	.	.	321 " —96·3	"	"	"	"
No pneumococci isolated	.	.	80 "				
			<hr/>				
			955 cases				

The results obtained in Types I and II cases were considered very

satisfactory, as unless the pneumococci are present in fair numbers the "Direct Test" cannot be expected to be 100 per cent. correct. If they are very scanty, as they may be in the early stages of the disease, and when it is remembered that only a small portion of the sputum is used, the reacting pneumococci might be easily overlooked. Type III results, on the other hand, were disappointing. The only excuse, apart from possible scantiness of the organisms, that is put forward is that at the beginning of this investigation the eye had been misled by the great size of the capsular reaction.

Although we were mainly concerned with the typing of cases of lobar pneumonia, the scope of our interest was gradually enlarged to include all kinds of pneumococcal lesions.

For our purposes, the pneumonias were divided into two groups:—

A. *Lobar Pneumonia*.

B. *Other forms of pneumonia*, such as broncho-pneumonia, influenzal pneumonia and so on.

The diagnosis entered in the books kept by the registrar was regarded as final. Unfortunately there were some cases registered as "Pneumonia" without any qualification and it was a moot point as to which group they should be placed. It must be admitted that the type isolated influenced us in this decision, but any error was probably small.

It was thought advisable to limit the lobar pneumonia results to the ten years—1931 to 1940, as towards the end of this decade the numbers began to fall, owing to institution of sulphonamide therapy. It should be mentioned that the great majority of our cases were adults.

#### GROUP A

##### *Lobar Pneumonia—Type Incidence*

	1931.	1932.	1933.	1934.	1935.	1936.	1937.	1938.	1939.	1940.	Average.
	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Type I	27.0	29.4	15.9	30.1	13.7	16.2	10.5	16.6	14.2	13.1	18.8
Type II	46.1	44.4	46.0	35.4	44.0	44.6	43.8	44.8	47.2	39.4	43.9
Type III	4.2	4.8	11.1	6.9	9.7	10.8	11.4	11.0	7.1	11.5	8.8
Group IV	22.7	21.4	27.0	27.6	32.6	28.4	34.3	27.6	31.5	36.0	28.5
Number of cases	141	126	126	116	175	130	105	181	127	61	Total 1288

##### *Lobar Pneumonia—Mortality Rate*

	1931.	1932.	1933.	1934.	1935.	1936.	1937.	1938.	1939.	1940.	Average.
	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Type I	7.9	19.0	20.0	11.4	20.8	28.6	27.3	16.7	...	12.5	15.7
Type II	35.4	42.6	38.0	46.3	36.4	39.7	45.6	33.3	8.3	4.4	34.1
Type III	33.3	50.0	57.1	75.0	41.2	42.8	50.0	35.0	33.3	42.6	45.1
Group IV	15.6	26.0	26.0	31.2	22.8	13.5	16.7	10.0	10.0	18.3	18.0

Typing sera for types 4 to 32 were obtained in 1938. We were then enabled to investigate 196 Group IV cases of lobar pneumonia with the following result.

Types	4	5	6	7	8	9	10	11	12	13	14	15	16
No.	24	21	11	24	31	4	6	4	6	3	3	2	4

Types	17	18	19	20	21	22	23	27	29	31	32	Higher types
No.	2	8	6	3	3	7	1	1	5	1	1	15

Types 4, 5, 7 and 8 represented 51 per cent. of the cases. This was an interesting and satisfactory result and conformed to experiences in the U.S.A.

To quote Finland, in 1942, "Types 4, 5, 7 and 8 are usually the most frequent of the Cooper types found in cases of typical lobar pneumonia."

## GROUP B

1931-1940. *Broncho-pneumonia and other Pneumonias*—238 Cases

	Types			Group IV.
	I.	II.	III.	
Incidence (per cent.)	4.6	15.5	9.2	70.6
Mortality rate (per cent.)	36.4	67.6	59.1	38.1

1931-1940. *Acute and Chronic Bronchitis*—54 Cases

	Types			Group IV.
	I.	II.	III.	
Incidence (per cent.)	2.0	7.4	22.2	68.4

1931-1945. *Empyema Thoracis*—277 Cases

	Types			Group IV
	I.	I.	III.	
Lobar pneumonia	50	33	6	24
Broncho-pneumonia	2	2	3	6
No associated lesion mentioned	38	17	8	27
Cases of lobar pneumonia, sputum typed, but not the empyemata	19	5	2	35
	109	57	19	92

The 35 Group IV cases, here, are an approximation, as on some occasions, when only a Group IV pneumococcus has been obtained from the sputum, subsequently an empyema has developed due to Type I or Type II.

Pneumococcal empyemata were also found in connection with bronchial carcinoma, gangrene of the lung, lung abscess, subphrenic abscess, and perforated duodenal ulcer, but merit no detail.

over biceps, and prelaryngeal. Apart from pneumonia there were various abscesses from different parts of the body :—

*Cerebral* (Type III and a Group IV), *Cerebellar* (Type III, and Type 13), *Neck* (3 Type III and one Type II), *Orbital* (Type 4), *Temporal* (Type III), *Scalp* (Type 5), *Abdominal wall* (Type 19), *Inguinal* (Type 8), *Lumbar* (Type III), *Buttock* (Type III), *Scrotum* (Type 6), *Bartholinian* (Types 18 and 21), *Thigh* (Type II), *Foot* (Type 8), *Pelvic* (Types 5 and 8), *Peritoneal* (Type 8), *Pyosalpinx* (Types II and 21), *Pyometra* (Type 13).

This completes our survey of pneumococcal infections in Edinburgh and district and we now append figures showing the type incidence of lobar pneumonia in many parts of the world.

### REMARKS

Attention is drawn to the fact that over a period of ten years, there was a marked preponderance of Type II lobar pneumonias over Type I cases, with the exception of one year, viz. 1934.

From the figures assembled from different parts of the world, Edinburgh seems to be rather exceptional in this respect, Type I pneumonias being the more prevalent, although in some cases there was an approximation between the two types, for instance, Glasgow.

In the case of empyemata, on the other hand, this position was reversed, the incidence of Type I cases being almost double that of Type II. The propensity of Type I pneumococcus to form empyemata is well known, but in the presence of such an excess of Type II lobar pneumonias here, such invasiveness is very remarkable.

The increased number of Group IV cases in broncho-pneumonia was to be expected. There was an increased mortality rate over that of lobar pneumonia.

The presence of Type III pneumococci to the extent of 70 per cent. in cases of otitis media and mastoiditis is noteworthy.

From the number of pneumococcal lesions cited the pneumococcus truly belies its popular name.

### SUMMARY

1. The type incidence in lobar pneumonias over a ten-year period, viz. 1931-1940, showed Type I 18·8 per cent., Type II 43·9 per cent., Type III 8·8 per cent. and Group IV 28·5 per cent.

2. The mortality rate was found to be Type I 15·7 per cent., Type II 34·1 per cent., Type III 45·1 per cent., and Group IV 18 per cent.

3. The Group IV cases in broncho-pneumonia and other pneumonias for the same period had increased to 70·6 per cent., with a mortality rate of 38·1 per cent.

4. In empyema thoracis, out of 277 cases, there were only 57 Type II cases as against 109 Type I.

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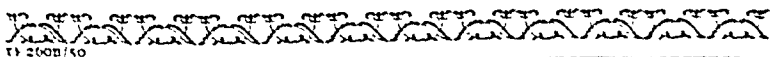
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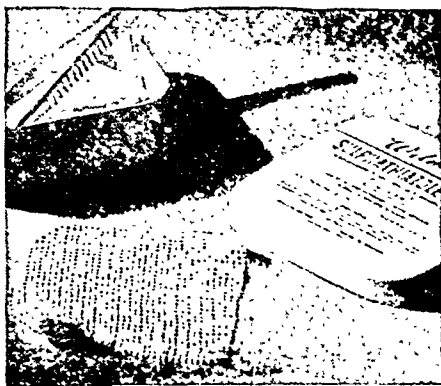
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5. Type III pneumococci were found 54 times out of 77 cases of otitis media and mastoiditis *i.e.* 70 per cent.

6. Pneumococci found in sundry conditions all over the body have been typed.

7. Type incidence of lobar pneumonias from world sources have been assembled.

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## ACROPARÆSTHESIA—AN IDIOPATHIC MYALGIA OF ELBOW

By M. G. GOOD, M.D., L.R.C.P. & S.Ed.

*(Hampstead General Hospital, London)*

RECENTLY F. M. R. Walshe (1945)<sup>1</sup> has drawn attention to the common well-defined syndrome that goes by the name of acroparæsthesia and is recognised as peculiar to women engaged in manual work, when they are in middle age, and especially when they are debilitated or fatigued. The author comes to the conclusion that acroparæsthesia is a mechanically produced syndrome, when from muscular atonia the muscles supporting the shoulder girdle allow these to drop to an abnormally low level leading to a rib-pressure syndrome. In this way a normal first rib, from which traction and compression are exerted on the lower component of the brachial plexus, and sometimes also on the subclavian artery, may be responsible for the complaints. The syndrome is not caused by a neuritis, and the only efficient treatment consists in rest.

According to others (Langdon-Brown and Evans, 1941)<sup>2</sup> acroparæsthesia is a vasomotor neurosis frequently associated with a neuropathic diathesis, a lowered vitality, inanition, anæmia, and pregnancy. Local causes are exposure to cold, particularly cold water, or to alternate cold and hot water as experienced by washerwomen. "The outlook regarding recovery is not good, but complications are not to be expected."

In 1940<sup>3</sup> the present writer described "idiopathic myalgia" as a muscular disease—idiopathic myopathy—of unknown origin, which is well defined and can be diagnosed by objective criteria. The disease, probably functional, is characterised by so-called "myalgic spots," localised in anatomical parts of a muscle, namely its origin, insertion, border or course or its appendages—tendon and ligaments. Pressure on a myalgic spot elicits an agonising wincing pain, accompanied by an involuntary reflex-like movement (jerking) in parts of the body not pressed upon, or the patient makes a grimace. This sign is pathognomonic.

The subjective symptoms are heterotopic or referred pain, often far away from the responsible myalgic spot, paræsthesia as numbness, pin-and-needles etc., especially in hands and fingers or feet and toes and paresis, diminished or temporary loss of power in a muscle or group of muscles, for example, dropping things from hands, giving way of knees, etc.

In my experience the syndrome of acroparæsthesia is most certainly due to an idiopathic myalgia of the elbow muscles, usually of the extensors and flexors of the wrist and fingers. Rarely the brachioradial

muscle is also affected. I propose to describe briefly here some cases seen by me in the last 4 months.

CASE 1.—Miss S. (35) has been suffering last two months from cold, "lifeless" left forearm and hand and pain localised in the ulnar and volar skin area. Myalgic spots located in the heads of the flexors originating from the internal epicondyle. After two treatments consisting in injection of 2 c.cm. of 2 per cent. procaine into the myalgic spots: no complaints. Diagnosis: internal cubital myalgia.

CASE 2.—R., housewife (55), complains of enervating paræsthesia, annoying discomfort and slight pain in right forearm. Diagnosis: cubital myalgia. After three injections of 2 c.cm. of procaine into the myalgic spots patient had no complaints.

CASE 3.—G. M., housewife (56). As a child she suffered from blanching of II-IV fingers, and pin-and-needles. For about a year repeated attacks of similar annoying character. Lately she developed agonising pain, especially at night and along dorsal radial surface of right forearm extending down to II-III fingers. Diagnosis: cubital myalgia. Cured by three injections of procaine.

Acroparæsthesia may be combined with rheumatism in other parts of the body, as in the following.

CASE 4.—G., teacher (57), frequent piano playing. For last eight years has been suffering from rheumatism and arthritis of spine. Present complaints: in addition to low backache and shoulder ache, agonising pain, pin-and-needles and formication along inner aspect of left forearm. Diagnosis: myalgia of elbow. Cured by injection of procaine.

The syndrome of acroparæsthesia is as a rule met in women of middle age or over, as stressed by most authors. But among many cases I have seen it in two men, both doctors and of middle or old age, as in the following case described in 1940.

CASE 5.—Doctor (51): severe dull pain in the right arm, especially on supination and pronation; handling a screw driver aggravated the pain to such an extent that work had to be stopped. In addition enervating paræsthesia along the forearm to the thumb and index finger, consisting in numbness, pin-and-needles and painful vibratory sensations. The pain was referred to a cutaneous area supplied by C<sub>5-7</sub>, of which C<sub>5-6</sub> innervate the brachioradialis and C<sub>6-7</sub> the extensor carpi radialis longus muscles. Diagnosis: myalgia of brachioradialis and extensor carpi radialis. Cured by physiotherapy applied to the myalgic muscular areas.

It is worth stressing that the modern diagnosis of myalgia, which was strictly defined in 1938,<sup>4</sup> is based on objective criteria and not on purely subjective sensations and tender spots, *i.e.* spots said to be tender on pressure by patients. "Idiopathic myalgia" does, therefore, not only satisfy the standard of an objective scientific diagnosis, but in addition is of great importance from the point of view of practical

therapeutics. All the complaints can be relieved and the patient cured in a short time by injection of 1-2 c.cm. of procaine into each myalgic spot.

*Summary.*—There is definite evidence for the claim that the syndrome of acroparæsthesia is due to an “idiopathic myalgia” of the elbow, affecting the origin and heads of extensors or flexors of wrist and hand. It is mostly met in women of middle age or older, but exceptionally in men of the same age. Appropriate and accurate injection of a few c.cm. of procaine cures the disease without delay.

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## NEW BOOKS

*Joseph Lister, The Friend of Man.* By HECTOR C. CAMERON. Pp. 176, with 13 illustrations. London: William Heinemann (Medical Books) Ltd. 1948. Price 17s. 6d. net.

This is a small book which tells of the more intimate side of Lister's life. It is written as a simple story and no attempt is made to elaborate any of his scientific work. It makes very interesting reading and gives a clear picture of the man with his fears, his happiness and in later life his sorrow and feebleness.

*Handbook for the Assistant Nurse.* By MARY E. SWIRE, S.R.N., S.C.M. Pp. x+308, with 211 figures. London: Baillière, Tindall & Cox. 1948. Price 10s. 6d. net.

This, the first book to be compiled especially for the assistant nurse, is by an author who has had considerable experience in teaching for this type of work. The syllabus is followed closely and the special needs of the aged and the chronic sick are stressed. The theoretical instruction including that on anatomy and physiology is the minimum needed for intelligent nursing, but for those intending to work in sanatoria more information would be essential.

Clarity and simplicity of both text and illustrations make the book suitable for its purpose.

*Surgical Pathology.* By PETER A. HERBERT, M.D. Pp. vi+710, with 410 illustrations. London: Henry Kimpton. 1948. Price 60s. net.

This book is not intended to be a detailed book on pathology. It has two aims. Firstly it provides a description of the earliest points of pathology for the surgeon without dealing with unnecessary detail. Secondly it is intended as a textbook for candidates for examination. To this end the subject has been treated from a regional viewpoint. Thus one chapter deals with diseases of the nose and throat, another with gynaecology, etc. As a reference book it is excellent. The illustrations are numerous and clear, and at the end of each chapter there is a most adequate bibliography. Each subject is introduced by a short description of its embryology and anatomy and this greatly enhances the usefulness of the work.

*Treatise on Surgical Infections.* By F. R. MELENEY, M.D. Pp. xvi+713. New York: Oxford University Press. 1948. Price 63s. net.

This is a remarkable book. It is the result of twenty years work and experience by the author who has practised both as surgeon and bacteriologist. It has been written essentially for the surgeon and its aim is to promote a high standard of sterile technique in the operating room. All surgeons experience from time to time unexplained and worrying wound infections which often spread rapidly round a ward. It is just such problems which are discussed in this book. Every aspect of infection is dealt with thoroughly. Ultra-violet radiation for air sterilisation is described fully and is recommended. Many tables of statistics are given. It is interesting to note that in 1925 14 per cent. of clean cases went septic. In 1942 the figure was 3 per cent. Silk is recommended for ligatures rather than catgut. Catgut is said to be a most common cause of infection. This book also contains a wealth of detail regarding bacteriological technique. There are many good illustrations and the photographs of the famous men associated with the subject, e.g. Lister, Koch and Pasteur, add to its attractions. It has been compiled during three definite stages of advance (i) before chemotherapy, (ii) during chemotherapy, (iii) during anti-biotic therapy. Dr Meloney may well be proud of this very considerable work.

*Essentials of General Cytology.* By R. A. R. GRESSON. Pp. ix+184, with 71 illustrations. Edinburgh: University Press. 1948. Price 21s. net.

This book is intended primarily for senior students of botany and zoology, and for teachers of biology to less specialised classes. Most of it is within the compass of the medical undergraduate, who will find it a helpful background to his study both of general biology and of human normal and pathological physiology. Medical readers in general who are interested in the applications of genetics to medicine, will find in it a useful summary of the essential cytological knowledge. For the physiologist and pathologist it is a very readable "refresher," and the bibliography will give them useful references for more detailed applications of cytology to their subjects. More consideration might have been given to the correlation of cell structure with cell physiology; some account of the histo-chemical work on the identification of intracellular enzymes would make an attractive addition to the book.

The illustrations and format are excellent.

*Techniques in Physiotherapy.* By F. L. GREENHILL, S.R.N., M.C.S.P. Pp. x+222, with 37 illustrations and 8 plates. London: Hodder & Stoughton. 1948. Price 12s. 6d.

This book is intended for practising physiotherapists and is in no way to be regarded as a textbook. It describes up-to-date physical methods in the treatment of a wide range of medical and surgical conditions, and, as is usual in books on physiotherapy, the problem of rheumatism is treated at considerable length. The author has obviously had a wide experience and she gives fairly detailed instructions as how to carry out the particular methods she advocates.

There are good chapters on the treatment of abdominal and chest conditions, and also a fairly detailed one on occupational therapy which should always be considered in conjunction with the standard physiotherapeutic procedures. The book is well presented and fully illustrated.

*Toxoplasmosis.* By Dr C. C. BINKHORST. Pp. 163, with 6 tables, 14 illustrations and 6 plates. Leiden: Stenfert Kroese. 1948. Paper covered 15s., Cloth 19s.

This excellent monograph reviews most comprehensively the literature and reported cases of this disease which is as yet unknown in this country. Bearing in mind, however, the wide distribution of the toxoplasma parasite in the animal kingdom and the frequency of its occurrence in man as shown by serological tests, it seems probable that we have here a cause of at least some unexplained eye lesions especially those in infants associated with retino-encephalopathy.

The book is illustrated with photographs of cases, and the X-ray plates and microphotographs showing the pathological changes of the disease are very well reproduced.

Altogether Dr Blinkhorst is to be congratulated on his collection and presentation of the facts concerning this little-known condition.

*An Atlas of Bone-marrow Pathology.* By M. C. G. ISRAELS. Illustrations by D. DAVISON. Pp. x+79, with 3 figures and 12 coloured plates. London: William Heinemann (Medical Books) Ltd. 1948. Price 30s. net.

The author claims "to provide an authoritative, accurately illustrated account of the bone-marrow in health and disease." This he achieves with fair success. The text is brief, but the descriptions are clear, and some useful tables are provided. Seven coloured plates illustrate types of cells, and there are coloured reproductions of representative fields from 20 actual marrow smears. The illustrations are drawings and have the slightly artificial appearance inseparable from this method; but they are much better than many such reproductions. Those who have to examine marrow smears will find the atlas a useful companion to more complete works on hæmatology.

*Occupational Medicine and Industrial Hygiene.* By RUTHERFORD T. JOHNSTONE. Pp. 604, with 107 illustrations, 7 in colour. London: Henry Kimpton. 1948. Price 50s. net.

Industrial medicine has now become a well-defined speciality and standard textbooks on the subject are beginning to appear. Dr Rutherford T. Johnstone of Los Angeles writes with authority and experience. One may confidently predict that this book will see many editions and will find a place on the bookshelves of specialists in industrial medicine on both sides of the Atlantic.

Two hundred and fifty-six pages are devoted to an excellent account of industrial toxicology. The general physician, wishing to learn about the possible toxic effect of any metals or chemicals, especially those recently introduced into industry, would be well advised to look first in this book. It is a reference work no medical library can afford to be without.

*Cancer.* I. Hérité—Hormones—Substances cancérogènes. By J. MAISIN. Pp. 248. Paris: Casterman. 1948. Price 84.00 francs.

This small volume is a general presentation of certain aspects of cancer, and, as the author says, it is written "pour les intellectuels non spécialisés dans la question du cancer." It opens with a short historical review of the occurrence of cancer from earliest times. There follow four chapters of which the first is an account of the well-known general features of malignant disease. Chapter two deals with heredity and cancer, and discusses the effect of environment—food, temperature, etc., and includes reference to Bittner's milk factor, etc. Chapter three is about the relations of hormones to cancer, and offers a good discussion of the various factors involved and the rather confusing evidence owing to the complexity and interaction of the various hormones. Chapter four is the longest section, on carcinogenic substances, and most space is naturally devoted to the derivatives of anthracene.

There is an extensive bibliography, covering 24 pages.

*General Cytology.* By E. P. D. DE ROBERTIS, W. W. NOWINSKI, and F. A. SAEZ. Translated by WARREN ANDREW. Pp. xi+345, with 143 illustrations and 18 tables. London: W. B. Saunders Company. 1948. Price 27s. 6d. net.

This book originally appeared in Spanish in Argentina in 1946. The present English edition is not a mere translation of the original work but a complete revision. It is an elementary textbook of general cytology and covers a wide field. As far as possible the functional significance of the recorded facts is stressed. Understanding is aided by brief descriptions of the latest methods employed in microchemistry, and of the application of new methods to the analysis of submicroscopic organisation. The illustrations and diagrams are clear and beautifully printed. The translation is good and only occasionally startles by a curious use of words or an excessive number of prepositions.

This book should be of interest to all those who know only a little of cytology and wish to know more. They will be stimulated, and grateful for the references at the end of each chapter.

*Recent Advances in Respiratory Tuberculosis.* By FREDERICK HEAF, M.A., M.D., F.R.C.P., and N. LLOYD RUSBY, M.A., D.M., F.R.C.P. Pp. vi+290. London: J. & A. Churchill Ltd. 1948. Price 21s. net.

It is eleven years since the last edition of *Recent Advances in Tuberculosis* by the late L. S. T. Burrell was published, and many changes of views and methods of investigation and treatment have taken place since then. As a result this is a new book and it bears the impression of the experienced authors. The book is no mere summary of the views of others. It is written with discrimination, is comprehensive in its scope, and succeeds in representing the advances and in being at the same time a compact textbook.



*Neurological Anatomy in Relation to Clinical Medicine.* By A. BRODAL, M.D.  
Pp. xv+496, with 94 illustrations. Oxford: Clarendon Press. 1948. Price 42s. net.

This book was originally published in Norwegian in 1943; a fact not without interest, and now the English translation is sponsored by a foreword from Professor le Gros Clark, but since the author comes from the same neurological school as Professor Monrad-Krohn he is assured of ready acceptance by English readers.

In many ways it is an unusual book, for it approaches the nervous system anatomy from a new angle, as indeed the title suggests. A correlation between clinical symptoms and anatomical lesions is the main aim of the work, and of course this implies the consideration of a certain amount of physiology. Research workers have been very active during the past decade or more in the fields of neuro-anatomy and neuro-physiology, and it is interesting to observe the skill with which Professor Brodal handles his material; at one time tending to dogmatise, but at others weighing up different theories with an unprejudiced mind.

It is obvious that the author is a master of the literature in his subject, and he includes a very extensive bibliography which provides the reader with an easy opportunity of pursuing his particular lines in more detail.

*Lung Dust Lesions, Pneumoconiosis versus Tuberculosis.* By L. G. COLE, M.D., F.A.C.R. Pp. xxii+474, with over 400 illustrations. White Plains, N.Y.: American Medical Films Inc. 1948. Price \$10.

The author of this monograph is a man of wide interests and a researcher of note. His major work has been as a radiologist but he has also acquired considerable skill as a histologist. With these two disciplines as a background Dr Cole has made an intensive study of pneumoconiosis. He has brought together a great wealth of material culled from his experience and from the literature. His book is very attractively illustrated both by radiological findings and by histological reproductions. The author himself admits that the full text is too voluminous for the casual reader and suggests a plan of approach which should approve adequate for all except the specialist student.

Dr Cole is to be congratulated on having made a valuable contribution to the knowledge of a very difficult subject.

*Memoirs of an Army Surgeon.* By J. A. R. Pp. 554. Edinburgh: Wm. Blackwood. 1948. Price 15s. net.

The author, a young Edinburgh surgeon, gives an account of his experiences during the recent war. He records his Odyssey from Britain to Egypt, along the north of Africa, across to Sicily and to various battle fronts in Italy, and later to Algiers, Marseilles and West Germany.

This is no mere day to day account of routine work, but a fascinating story which should be of special interest to medical men.

*Critical Studies in Neurology.* By F. M. R. WALSHE, M.D., F.R.S. Pp. xv+256, with 16 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 15s. net.

This is a stimulating book. All studies made by the author whether in neurology or in general affairs are invariably critical, and this is probably, why his writings are so eagerly read. Many therefore will be familiar with the articles in the present volume, since they have all appeared separately in recent years, but it is convenient to find them in compact form. In no sense a bedside book, the reader must have his wits about him since every paragraph, indeed almost every sentence requires contemplation.

In these days of mechanical fascination and its dehydrating effect on the clinician, Dr Walshe does an inestimable service as a corrective.

*Tuberculosis of the Knee Joint.* By JOHANNES MORTENS. Pp. x+550. Copenhagen : Einar Munksgaard. London : H. K. Lewis & Co. 1948. Price 63s. net.

This book is a monograph on tuberculosis of the knee joint. Much of it, particularly the section dealing with surgical treatment, is historical, but pathogenesis, pathology, differential diagnosis, and treatment are dealt with in detail. It is based on an exhaustive study of the literature and on 181 cases of chronic affections of the knee, 114 of which were ultimately found to be tuberculous, which the author has followed up over a period of twenty-five years. The subject of differential diagnosis is handled carefully and the value of diagnostic arthrotomy, and its fallacies, are discussed. It is interesting that 38 cases fell into categories which the author labels gonitis incertæ causæ and gonitis chronica simplex. His views on treatment are much the same as those held in this country. Stress is rightly laid on the value of conservative and general treatment, but the part which timely surgery can play, and its necessity in most cases of the disease in adults, are emphasised.

*Pathology.* Edited by W. A. D. ANDERSON, M.A., M.D., F.A.C.P. Pp. xii+1453. with 1183 illustrations and 10 colour plates. London : Henry Kimpton, 1948. Price 75s. net.

To attempt to review this work in detail would involve a minor treatise on pathology. Under the editorship of Professor Anderson of Wisconsin, who contributes 11 chapters of the total of 46, there are 31 other contributors, all well known, from various American departments of pathology.

The orthodox order has been maintained of "general" and "special." After an introductory chapter, there are 18 on general pathology followed by 26 on special pathology of the various systems, with a final chapter on "Heredity and Constitution in Disease."

In the general section, considerable space is given to injuries due to physical agents, chemical substances and to radiation effects; amongst these the lesions due to atomic bombs are described in detail. Rickettsial and viral diseases form an up-to-date chapter somewhat condensed into 44 pages, while much space is given to Fungus Infections, and Protozoal and Helminthic Infections.

The number of pages is not a fair indication of the content, as the greater part of the print is in small type, which makes possible more subject matter per page but is a little trying to the reader. At the end of each chapter is an extensive bibliography, though, perhaps naturally, the references from American sources preponderate.

The illustrations are numerous and, on the whole, clear and instructive.

This is a valuable contribution from the American schools of pathology, and both the editor and his contributors are to be congratulated on producing a work which should be useful for reference by both clinicians and pathologists.

*Dictionary of Genetics.* By R. L. KNIGHT, D.SC., PH.D., A.I.C.G.A. Pp. 183. Waltham, Mass., U.S.A. : Chronica Botanica Co. London : Wm. Dawson & Sons. 1948. Price \$4.50.

Because genetics is a young science, its workers have often to coin their own technical terms and unfortunately there are sometimes several words to express the same idea. There is much to be said in favour of simplifying genetic terminology, and the existence of an authoritative work such as this should help to avoid further confusion.

The dictionary is not limited to modern introductions, for it is still necessary to record and understand the older literature of the subject. Hence the appearance of such familiar words as rogue, kindred and tribe amongst the more recent introductions. A series of appendices contain mathematical formulæ and tables of use to the geneticist.

This well-produced work should have an important influence on future literature on genetics and allied subjects.

*Mycoses and Practical Mycology.* By N. GOHAR, M.R.C.S., L.R.C.P. Pp. xi+234, with 4 coloured plates and 134 illustrations. London: Baillière, Tindall & Cox. 1948. Price 25s.

A warm welcome must be extended to an authoritative work on a subject so long neglected by the medical profession, for it is increasingly recognised that fungi play a considerable part in general medicine as well as in dermatology and tropical medicine.

Dr Gohar devotes two chapters to the general principles of mycology and the mycoses, then he deals successively with lesions affecting various regions of the body, and finally there is a very helpful account of fungicides, useful prescriptions and culture media. Emphasis is laid on the clinical features of the disease although the laboratory and botanical aspects are not altogether neglected.

The book is well written, excellently produced and can be thoroughly recommended.

*Modern Methods of Infant Management.* Edited by W. R. F. COLLIS, M.A., M.D., F.R.C.P., F.R.C.P.I., D.P.H. Pp. vii+285, with 65 illustrations. London: William Heinemann (Medical Books) Ltd. 1948. Price 17s. 6d. net.

This excellent and practical little volume covers the whole field of infant management from antenatal care to the end of the first year of life. It is divided into four sections: the first deals with antenatal care and the hygiene of birth, the second and third are mainly concerned with the problems of breast and artificial feeding, the fourth with other problems related to the newborn babe, and discusses briefly some pathological conditions, both medical and surgical, which occur during the first few months of life. The text is clear and concise, yet very readable. The methods described are those in common use at the Rotunda hospital.

This little book can confidently be recommended to all who are interested in infant management.

*Emergencies in Medical Practice.* Edited by C. ALLAN BIRCH, M.D., F.R.C.P. Pp. xi+468, with 113 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 25s. net.

This book deals with the management and treatment of "medical" emergencies. Much useful information is to be found in its pages. The sections on cardio-vascular and renal emergencies and on gastro-duodenal hæmorrhage are models of clarity. The treatment of mushroom poisoning is a valuable feature. In general the standard in the different sections of the book is varied. Under "epistaxis" the post-choanal pack technique is inadequately described and "Trotter's method" of treatment receives no mention. There is contradictory advice on the use of adrenaline and pituitary in the treatment of "shock" in the "respiratory" and "cardio-vascular" sections.

The book is beautifully produced and the illustrations make a pleasant presentation, if not always useful.

*Textbook of the Rheumatic Diseases.* By W. S. C. COPEMAN, O.B.E., M.D., F.R.C.P. Pp. viii+612, with 351 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 50s. net.

The medical and social importance of rheumatic disease in this country has only been appreciated during the past twenty years. The ætiology, clinical features, diagnosis and treatment of these conditions have therefore stimulated increased interest, and much research is at present being carried out. There is at present no textbook which embraces general medicine, rheumatism, orthopædics and physical medicine; subjects in which the specialist in rheumatology must be thoroughly acquainted. The editor and other distinguished contributors have produced such a book. This book should prove of great value to both general physician and those especially interested in rheumatism.

## NEW EDITIONS

*A Handbook of Orthopædic Surgery.* By A. R. SHANDS, Jr., B.A., M.D., and R. B. RANEY, B.A., M.D. Third Edition. Pp. xviii+574, with 159 illustrations. St Louis: The C. V. Mosby Company. 1948.

This is a concise and eminently readable, short textbook of orthopædic surgery, and is intended primarily for the undergraduate, and the general practitioner.

The scope is comprehensive, and all the important orthopædic conditions are dealt with adequately.

The text is well illustrated, but no photographs or X-ray pictures have been reproduced directly; the author having preferred to have these redrawn to emphasise characteristic features. Many clinical and X-ray photographs are sufficiently characteristic of themselves, and a number might have been included without redrawing.

*Introduction to Diseases of the Chest.* By JAMES MAXWELL, M.D., F.R.C.P. Third Edition. Pp. 11+307 with 66 illustrations. London: Hodder & Stoughton Ltd. 1948. Price 12s. 6d. net.

This third edition of Maxwell's *Diseases of the Chest* attains the same high standard as the earlier publications of this book. The volume is divided into four main sections—history, physical examination, special investigations, and diseases, with in addition some sixty-two X-ray illustrations of first class quality.

The whole book displays a profound understanding of the subject by one who has accumulated vast clinical experience over the years, and who has given mature consideration to the most modern methods. Entitled by the author as an introduction to this special branch of medicine, there is nevertheless a wealth of valuable material to be found in all its pages. The volume is compact, easy to handle, well turned out, and merits the highest commendation. This book can be strongly recommended as a standard work to any who are interested in the study of diseases of the chest.

*An Introduction to Surgery.* By RUTHERFORD MORISON, F.R.C.S., and CHARLES F. M. SAINT, F.R.C.S. Fourth Edition. Pp. 243, with 304 illustrations. Bristol: John Wright and Sons Ltd. 1948. Price 42s. net.

Rutherford Morison, who first wrote this book, taught and stressed the general principles of Surgery above all else. Once the student had grasped these principles the detail could be examined and understood readily. Therefore it is not surprising that the first half of the book is devoted to such basic processes as shock, hæmorrhage, infection and gangrene. It is a short book, easy to read, and has good illustrations. The student is helped to realise that many different organs in the body suffer from the same fundamental pathology. He is discouraged from the common mistake of dividing the body into little compartments and of studying each separately.

*Physicians Handbook.* By JOHN WARKENTIN, PH.D., M.D. and J. D. LARGE, M.S., M.D. Fifth Edition. Pp. 293. Palo Alto, California, U.S.A.: University Medical Publishers. 1948. Price 2 dollars.

In this, the fifth edition, of this little handbook the authors have given further emphasis to the importance of clinical features in disease and their correlation with laboratory findings. This book summarises clearly yet concisely the diagnostic procedures and laboratory methods which the physician may be called upon to perform. In addition a section on post-mortem technique and the treatment of acute poisoning has been included and makes this a most valuable and serviceable handbook.

*Demonstrations of Physical Signs of Clinical Surgery.* By HAMILTON BAILEY, F.R.C.S. Eleventh Edition. Part IV. Pp. 426, with 657 illustrations. London: John Wright & Sons Ltd. 1948. Price 8s. 6d. per part.

This fourth part completes the eleventh edition of this attractive book, which has proved so popular with undergraduates. The illustrations—two or more on every page—are excellent. The colour photographs are of a very high quality.

*Physical Signs in Clinical Surgery.* By HAMILTON BAILEY, F.R.C.S.ENG. Eleventh Edition. Parts II and III. Bristol: John Wright & Sons Ltd. 1948. Price 8s. 6d. per part.

Within five months have appeared the first three parts of this work, now in its eleventh edition. It therefore seems probable that the complete work will be published soon. Many books have been written by this author, but none better than these demonstrations. It will be said by many that the bedside is the only place to teach physical signs, but few can deny, after reading these books, that the demonstrations are very real. The illustrations with their accurate colouring and markings are of an excellence rarely found in textbooks. These books are very popular with students, especially those in crowded medical schools where it is often difficult to provide adequate clinical material for inspection.

*A Handbook of Ophthalmology.* By HUMPHREY NEAME, F.R.C.S. and F. A. WILLIAMSON-NOBLE, F.R.C.S. Sixth Edition. Pp. x+336, with 12 plates containing 46 coloured illustrations and 189 text figures. London: J. & A. Churchill Ltd. 1948. Price 21s.

This book is written primarily for general practitioners and undergraduate students. In its relatively small compass a comprehensive survey is given of ophthalmic disease. Starting with a description of the technique of examining the eye, attention is directed mainly to diagnosis and treatment of commoner diseases, particularly those occurring in hospital out-patient practice.

The plates and diagrams are excellent, illustrating the text most satisfactorily. This book deserves a place on the bookshelf of all medical practitioners.

*Principles of Full Denture Prosthesis.* By E. WILFRED FISH, C.B.E., M.D., D.D.SC., F.D.S. Fourth Edition. Pp. 140, with 59 illustrations. London: Staples Press. 1948. Price 15s.

This well-known book, which made its first appearance in 1933, deals with the principles which govern the stability of full dentures. Its popularity among busy practitioners lies in the fact that descriptions of elaborate techniques are omitted and the text is confined to the fundamentals upon which any successful full denture technique is based.

The general scheme of the book remains the same as in previous editions. The first section of each chapter deals with theoretical considerations and is followed by an account of the practical application of the principles involved.

Chapter V has been re-written and enlarged and describes a new approach to the problems of determining the position of the artificial teeth in relation to the face and jaws, both in the newly edentulous patient and in the older patient where resorption has destroyed many of the anatomical landmarks. This chapter also includes a survey of the difficult problem of remodelling old dentures which have ceased to function properly and emphasises the importance of tongue-space.

Other additions to the text are to be found in Chapter IV on the "Impression Surface."

The illustrations are good and their arrangement is an improvement on previous editions. The inclusion of a reference summary is another useful feature.

The printing and binding are excellent for such a moderately priced book and the author and publishers are to be congratulated on their work.

*Diseases of the Nose and Throat.* By Sir ST CLAIR THOMSON, M.D., F.R.C.S., and V. E. NEGUS, M.S., F.R.C.S. Fifth Edition. Pp. 1004, with 13 colour, 20 radiographic and 11 other plates and 369 figures. London: Cassell and Company, Ltd. 1948. Price 70s. net.

Mr Victor Negus must be congratulated upon a very great achievement in moulding the recent advances in the speciality into the existing framework, while at the same time maintaining a careful balance between old and new. The rearrangement of the various operations in their appropriate section has added to the clarity of the work. A new chapter is devoted to sinusitis in children and laryngismus stridulus has found its correct place among the neurological diseases of the larynx. Diseases of the lung and endoscopy in general has been expanded and has been dealt with in three parts. The illustrations of pathological specimens and microphotographs are of inestimable value in a book of this nature. The chapter on treatment, both local and general, is up to date and sound in conception. The sections dealing with malignant disease are masterly in their handling of the subject.

This book will be recognised as the authoritative book of reference on diseases of the nose and throat.

*Abdominal Operations.* Second Edition. By RODNEY MAINGOT, F.R.C.S.ENG. Pp. xxiii+1274, with 468 illustrations; large royal 8vo. London: H. K. Lewis & Co. Ltd. 1948. 84s. net.

This work represents no mere description of operative technique. It deals also in detail with the ætiology, pathology and clinical features of all lesions of the abdominal viscera, the choice of operation, pre- and post-operative treatment, together with most complications that may occur. In short—it is a comprehensive treatise covering all aspects of abdominal surgery.

Much of the original text has been rearranged or expanded, and new sections have been added to cover such subjects as vagotomy, cardiospasm, congenital intestinal obstruction, synchronous abdomino-perineal excision of the rectum, diaphragmatic hernia and portal hypertension.

Mr Maingot is to be congratulated on having brought this comprehensive work so thoroughly up to date. He has had the assistance of eight distinguished contributors. The book is beautifully produced, its two-colour binding being a pleasing innovation. It should be assured of a warm welcome from general surgeons throughout the English-speaking world.

*Neuroanatomy.* By FRED A. METTLER, A.M., M.D., PH.D. Second Edition. Pp. 536, with 357 illustrations, including 33 in colour. London: Henry Kimpton. 1948. Price 50s. net.

This handsome volume comes from the Department of Neurology, Columbia University, and the fact that a second edition is already available is a measure of its popularity among students for whom it is primarily intended.

The essential subdivision remains the same, the first part dealing with appearances as seen with the naked eye, while the second part of the work is the microscopic section which aims at establishing a sound and usable functional viewpoint. Great care has been taken to define terminology with the result that much potential confusion has been obviated; a confusion indeed that in past writings on the subject has often offset the advantage of otherwise excellently written descriptions. But an outstanding feature of the work is the wonderful effort that has been made with the illustrations. While a number of these are undoubtedly old friends, yet one marvels at the skill with which each has been chosen to suit the text, and the coloured ones are considerable works of art and must make an instant appeal to those who are visualists; that is in this speciality at least, the majority.

Opportunity has been taken to introduce new concepts, and bring the large bibliography up to date. Undoubtedly this new edition is assured of bringing the work further success and popularity.

*The Clinical Examination of the Nervous System.* By G. H. MONRAD-KROHN, M.D.OSLO, F.R.C.P.LOND. Ninth Edition. Pp. xx+459, with 131 illustrations. London: H. K. Lewis & Co. Ltd. 1948. Price 16s. net.

Basing this book on personal experience gained in his own clinic, the author sets out to describe his methods for the benefit of fellow clinicians. He includes mainly tests which he has found useful, and it is interesting that many of these have remained unchanged since the first edition 27 years ago.

Advances in neurological examination and additional procedures, notably electroencephalography and angiography, which have become increasingly important, find a section in the large Appendix.

This volume remains a valuable guide to those who deal with nervous disease in clinics and wards.

*Pharmacology.* By J. H. GADDUM, F.R.S., SC.D., M.R.C.S., L.R.C.P. Third Edition. Pp. xvi+504, with 75 figures. London: Oxford University Press. 1948. Price 25s. net.

The third edition of Professor Gaddum's textbook has been considerably enlarged by additions and alterations. Among the new sections introduced are those dealing with folic acid, antihistamine drugs, BAL, the newer insecticides and streptomycin. The book contains a wealth of information, considerably more than would be required of the student, much of it of interest to the post-graduate. The chapter on general pharmacology, which includes a description of methods of biological assay and statistical analysis, is particularly valuable.

*A Textbook of Clinical Pathology.* Edited by F. P. PARKER, M.D. Third Edition. Pp. 1024, with 229 illustrations. Baltimore: The Williams and Wilkins Company. 1948. Price 50s. net.

The chapters on Blood Groups and on Hormones and Vitamin Assay have been largely re-written. Biochemical technique too has been brought up to date, particularly in those sections dealing with the estimation of cholesterol, proteins and phosphatase.

The typing of pneumococci occupies more space than its present clinical importance warrants, whereas the examination of the sputum for malignant cells receives but passing reference. Liver biopsy too is omitted, presumably on the ground that it is more within the sphere of the biologist.

One might suggest that detailed description of an impressive number of laboratory tests has left too little room for discussion of their selection and clinical interpretation.

*Pulmonary Tuberculosis.* By G. C. KAYNE, W. PAGEL and L. O'SHAUGHNESSY. Second Edition. Pp. xviii+720, with 268 illustrations. London: Oxford University Press. 1948. Price 63s.

The first edition of this book appeared in 1939 and the intervening years have witnessed the untimely deaths of Gregory Kayne and Laurence O'Shaughnessy. The present edition bears the names of W. Pagel, F. A. H. Simmonds, N. Macdonald and L. Fatti and is in many aspects a new work. Dr Pagel has expanded his important sections on pathogenesis and pathology. He writes from wide experience based on his own extensive pathological investigations. Perhaps the most interesting section is that which deals with the lesions and immunological problems of the chronic disseminating phase which he was among the first to study critically. His style is not easy but his material and argument repay careful study. There are excellent detailed sections on diagnosis, prognosis, prevention and epidemiology, and an appendix on antibiotics and chemotherapy. The chapters on management, which comprises all forms of treatment including the various forms of collapse and extirpation, are, by their critical accuracy, conciseness, and lucidity, probably the finest presentation of this aspect of the subject to be found in any textbook. This edition enhances the already high reputation of the work.

*Psychobiology and Psychiatry.* A Textbook of Normal and Abnormal Human Behaviour. By WENDELL MUNCIE, M.D. Second Edition. Pp. 620, with 70 illustrations. London: Henry Kimpton. 1948. Price 45s. net.

The first edition of 1939 contained 182 pages of bibliographic appendices surveying the historical development of the concepts of the principal "functional" psychiatric states: these appendices are now omitted. There are a very few additions to the first part, but these include new chapters on psychosomatic symptoms and on the special physical methods of treatment. Many additions have been made throughout the rest of the book, to bring it up to date. This is an interesting book, based upon Dr Adolf Meyer's general psychobiological principles. We think, however, that it is much too long for easy reading and could, with great advantage, have been condensed.

*The Natural Development of the Child.* By AGATHA H. BOWLEY, PH.D. Third Edition. Pp. xvi+190, with 84 photographs. Edinburgh: E. & S. Livingstone Ltd. 1948. Price 8s. 6d. net.

This book on the psychological development of the child, written by a school psychologist of high standing who has had experience in general and nursery school teaching, is intended primarily for school teachers and parents. The author discusses in simple language the intellectual, social and emotional aspects of normal psychological development, and of psychological disorders, in the various age periods of childhood including adolescence. Liberal illustration with case histories and photographs imparts a feeling of greater reality, and the extensive bibliography is commendable.

*Enuresis.* By R. J. BATTY, M.D., B.SC., D.P.H. Second Edition. Pp. 103, with 9 illustrations. London: Staples Press Ltd. 1948. Price 9s. 6d. net.

This monograph is based on the author's experience with almost one thousand cases of enuresis. He emphasises the diversity of circumstances which cause the disease. In his series threadworms were the commonest organic cause and poor social conditions the principal psychogenic cause. He stresses the paramount importance of a detailed history and thorough examination, and also the value of a home visit and a school teacher's report. Such care ensures a logical approach to treatment, in which drugs play a small part.

The book contains much valuable information for all who treat this disease.

*Human Embryology and Morphology.* By Sir ARTHUR KEITH. Sixth Edition. Pp. xii+690, with 578 text figures. London: Edward Arnold & Co. 1948. Price 40s. net.

The appearance of a new edition of this well-known textbook is particularly welcome. Sir Arthur Keith is to be congratulated on the amazing feat that he has accomplished in keeping pace with the ever-increasing output of published work ranging over an extremely wide field. To the younger generation of embryologists and morphologists keeping track of new advances, even over a limited field is an ever present difficulty, yet Sir Arthur appears to have accomplished this with his usual delightful presentation over the whole field of embryology, including up-to-date statements on the experimental aspects of the subject.

It is pleasing to find in the new edition expositions and judicious comments upon such items of recent controversy as the human premaxilla and the role of the neural crest. Much new discussion has been added relative to the development and morphology of the central nervous system and the special sense organs, especially the eye. Other useful sections deal with the hypothalamus, the "pubic apron," inter-sexual conditions, bone growth, the development of joints and Streeter's "foetal aplasia." This work can be very confidently recommended as one that combines in unique fashion the aspects of human anatomy indicated in its title.



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# HEART DISEASE COMPLICATED BY PREGNANCY

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THE material on which this paper is based has been accumulating over the past twenty years. In 1928 a Cardiac Clinic was started in conjunction with the Ante-Natal Department of the Royal Maternity Hospital. A preliminary report based on the first 95 patients observed in that Clinic was presented to this Society in 1931 (Gilchrist, 1931).

## The Transactions of the Edinburgh Obstetrical Society

SESSION CI.—1948-1949

Years.	Total Admissions.	Total Deaths.	Maternal Mortality per cent.	Total Cardiac Cases.	Percentage Incidence of Organic Heart Disease.	Total Cardiac Deaths.	Cardiac Deaths as percentage of Cardiac Cases.	Cardiac Deaths as percentage of Total Maternal Deaths.
1928-32	18,359	203	1.11	205	1.12	13	6.3	6.4
1933-37	16,499	159	0.96	228	1.40	17	7.5	10.7
1938-42	20,015	125	0.62	266	1.33	9	3.4	7.2
1943-47	25,549	69	0.27	401	1.58	7	1.7	10.2
1947	5,944	11	0.18	106	1.80	1	0.9	9.1

four five-year periods from 1928, when the Cardiac Clinic commenced work. The table shows the steady increase in the number of cardiac patients attending the Clinic and a mounting incidence of organic heart disease detected in pregnant women. It is true that this may be partly fictitious as a result of the greater interest in heart disease and in consequence a greater number of patients are referred for an opinion to the Cardiac Clinic. More than a hundred new patients attend the Clinic each year, whereas twenty years ago about forty women attended yearly. Although the numbers are greater, it is

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noteworthy that the deaths from heart disease are falling progressively. In our first five-year period (1928-32) 13 of 205 cardiac women died (6.3 per cent.), whereas in the last five-year period (1943-47) 7 of 401 patients (1.8 per cent.) succumbed to this cause—a more than threefold reduction in cardiac mortality. Indeed, for the year 1947 there was only one cardiac fatality amongst 106 women, the subjects of organic heart disease.

It may be argued that this striking reduction in the cardiac death-rate is part and parcel of the very creditable fall in the hospital's total maternal mortality apparent over the past twenty years. The outstanding advances in the control of the pyogenic infections, in the care of the toxæmias and in the treatment of hæmorrhage, have together brought about a fall in the overall maternal mortality from 1.11 per cent. in the years 1928-32 to 0.18 per cent. in 1947. It is true that the cardiac women must have shared the benefits of these newer therapeutic measures. Nevertheless, cardiac disease now plays a larger part in the total maternal mortality than it did twenty years ago. Table I shows that 5.9 per cent. of the total maternal deaths in the first five-year period were attributable to this cause. It therefore appears that proportionately more women are dying of rheumatic heart disease than formerly.

Closer analysis reveals that this figure is less unsatisfactory than might appear at first sight. Had there been no improvement in the care of pregnant cardiac women over the past twenty years and their death-rate therefore maintained at approximately 6 per cent. or more, as it was in 1928-32, then of the 106 patients observed in our series during 1947, 7 of these women would have been expected to die in place of the single fatality actually recorded. Under these circumstances the proportion of cardiac deaths to total maternal deaths would have amounted to approximately 40 per cent. instead of the 9 per cent. actually recorded.

It may therefore be concluded that, though cardiac disease takes a more prominent place in the production of maternal fatalities than it did twenty years ago, the methods now advocated in the care of cardiac women during pregnancy and labour are proving increasingly effective. The figures presented go to show that the reduction in the maternal death-rate from rheumatic heart disease, which has been recorded during the past twenty years, makes itself a substantial contribution to the overall fall in the maternal mortality rate now being recorded. Better care of the cardiac women will produce further improvement—indeed, it ought to be possible to reduce the maternal deaths from this cause to negligible proportions.

Through the courtesy of the Obstetrical Registrars of the Maternity Hospitals of Glasgow, Liverpool and Manchester, we have been able to compare our Edinburgh results over the past twenty years with those obtained at these large centres. Table II shows that in these four centres, which may be taken as representative of this country, there has been a general reduction in maternal mortality from organic

heart disease in the last twenty years; both for "booked" and "non-booked" cases all centres show improvement. As might be anticipated, the mortality rate for those cardiac women admitted to the hospital as emergencies, or who have received no ante-natal care for one reason or another, is on the average three times as high as amongst those women supervised at the Cardiac Clinic and admitted to hospital a day or two before labour is due. Averaging the series (Table II) it appears that the mortality rate has been reduced by approximately one half for "booked" cases when the first and second ten-year periods are compared, and amongst "non-booked" cases by a third in the twenty years under review. Supervision throughout pregnancy therefore means much to these women. If further reductions in the death-rate are to be obtained, earlier use must be made of the services of the cardiologist.

To direct attention to the figures of the individual centres, it is perhaps sufficient to point out, as Table II shows, that in Edinburgh

TABLE II

*Showing Incidence and Mortality Rates of Cardiac Cases in Different Centres over a Period of Twenty Years Divided into Two 10-year Periods*

Centre.	Cardiac Pregnancies.		Mortality Rate per cent.			
	Total No.	Per cent. Incidence of Total Pregnancies.	Booked Cases.		Non-booked Cases.	
			1st 10 yrs.	2nd 10 yrs.	1st 10 yrs.	2nd 10 yrs.
Edinburgh . .	1100	1·3	3·5	1·7	12·6	4·4
Glasgow . .	2183	2·4	4·3	2·8	9·8	7·5
Liverpool . .	730	1·7	3·7	2·2	5·4	6·2
Manchester . .	1401	2·9	4·5	1·4	7·7	5·4

for the first ten-year period the mortality rate amongst "non-booked" cardiac women was the highest of the four. The reduction in the second ten-year period to a mortality rate of 4·4 per cent., as compared with 12·6 per cent. in the preceding decade, is more creditable and is, we believe, the result of the emphasis put on the doctrine of "non-intervention." When congestive failure has been brought under control by energetic medical measures, the obstetrical problem is at once simplified and labour as a rule may be allowed to proceed. Needless interference increases the mortality rate.

#### THE DIAGNOSIS OF HEART DISEASE IN PREGNANCY

It would be outside the scope of this paper to elaborate the methods employed in the recognition of the different varieties of organic cardiac lesions. In the child-bearing period rheumatic heart disease predominates and therefore evidence of a valvular flaw is common. In a consecutive series of 315 cardiac women the ætiological factors responsible for the heart disease as determined during pregnancy are presented in Table III. Of these women 94 per cent. were regarded as suffering from rheumatic heart disease. Although hypertension is

common, hypertensive heart disease is comparatively rare and syphilitic heart disease most unusual in the fertile years. The increased interest shown in congenital heart disease in recent years has resulted in the more frequent recognition of different varieties of this form of heart disease in pregnant women.

Valvular disease is productive of distinctive physical signs which, however, can prove most deceptive during pregnancy. The increase in heart size, the common systolic murmur both at the apex and at the base, the radiological pattern of an enlarged left auricle, are features commonly found in pregnancy, all of which can readily mimic mitral disease when none in fact exists. Confusion is increased by the undoubted tendency of many pregnant women to experience a minor grade of exertional dyspnoea and to show quite commonly a trace of oedema about the feet and ankles. The borderland between the physiological adaptations of the healthy heart and the early signs of myocardial insufficiency as manifested by the rheumatic heart is not sharply defined. There should therefore be hesitancy in diagnosing rheumatic heart disease unless the auscultatory signs are definite and

TABLE III

*Showing Percentage Distribution of the Different Varieties of Organic Heart Disease Encountered amongst 315 Cardiac Women During Pregnancy*

Etiology.	Incidence per cent.
Rheumatic heart disease . . .	94.0
Congenital heart disease . . .	3.6
Hypertensive heart disease . . .	1.8
Miscellaneous . . . . .	0.6

conclusive. Most difficulty occurs in the presence of a systolic apical murmur, slight limitation of physical activity, a trace of evening oedema and a radiological pattern such as that shown in Figs. 1 and 2. A healthy heart during pregnancy may display the mitral configuration (Hollander and Crawford, 1943).

Repeated clinical examinations are necessary. It is not sufficiently realised that during pregnancy the characteristic murmurs of mitral stenosis may vary appreciably from day to day, being present on one occasion and absent the next. The organic lesion can be overlooked. Even more readily, the functional adaptations of the heart to the growing foetus may be attributed to organic disease. Emphasis must be placed on repeated search for known organic signs of valvular disease—in particular the soft blowing diastolic murmur of aortic regurgitation, heard best at the fourth left interspace close to the sternum when the patient stops breathing at the end of a deep expiration, and the mid-diastolic murmur of mitral stenosis with a snapping first sound maximum in intensity at or just outside the apex beat in the left lateral position.

Coarse murmurs, usually systolic in time, often accompanied by thrills maximum at sites other than recognised valvular areas, point

to congenital flaws. In this connection attention may be directed to the association of brachial hypertension with weak or absent femoral pulses, which, with notching of the ribs, gives the clue to coarctation of the aorta. More and more examples of this congenital defect are now being recognised in pregnant women.

### THE ASSESSMENT OF THE RISK

Experience has shown that in judging of the ability of the cardiac woman to go successfully to term there are three main factors to consider, which in order of importance are (1) the functional grade—a measure of myocardial capacity, (2) the age of the patient, (3) her previous circulatory experience in a preceding pregnancy. Admittedly, other factors play a part: for instance, the patient's ability to co-operate in the advice given her at her attendance at the Clinic, her willingness to submit to perhaps prolonged periods of in-patient care before her confinement, her successful avoidance of upper respiratory tract infections and of the hypertensive toxæmias, both of which are of even more serious consequence to the woman with pre-existing rheumatic heart disease in that either may precipitate acute pulmonary oedema or congestive heart failure when otherwise unanticipated.

The size of the heart and the presence of single or multiple valvular flaws are not in themselves of great consequence. Disturbances of cardiac rhythm have long been regarded with disfavour in judging of the cardiac woman's prospects. Auricular fibrillation in the subject of rheumatic heart disease is to be regarded as an indication that the patient has reached an advanced stage in the degenerative process and is therefore more liable to congestive failure.

(1) *The Functional Grade.*—Twenty years' experience of the application of this method of classification of myocardial efficiency emphasises its undoubted value. It has received the whole-hearted support of the great majority of workers experienced in obstetric cardiology (Jensen, 1938, 1940).

It is recommended that the patient, when she first comes under observation, should be placed in the appropriate grade, according to the following scale, as formulated by the New York Heart Association (1939):—

Grade I is composed of patients with cardiac disease and no limitation of physical activity. Ordinary physical activity causes no discomfort. Patients in this class do not have symptoms of cardiac insufficiency nor do they experience effort pain. As a general rule the presence of organic heart disease has been recognised in the course of a routine examination.

Grade IIa is composed of patients with cardiac disease and slight limitation of physical activity. They are comfortable at rest. When ordinary physical activity is undertaken, discomfort results in the form of fatigue, palpitation or breathlessness. As a general rule they have themselves come to avoid heavier household duties.

Grade IIb is composed of patients with cardiac disease and marked limitation of physical activity. They are comfortable at rest, but discomfort in the form of undue fatigue or breathlessness is caused by less than ordinary

activity. They commonly show a trace of œdema about the ankles towards evening.

Grade III is composed of patients with cardiac disease who are unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency are present even at rest. They present evidence of congestive heart failure.

Patients in Grades I and IIa need give rise to little concern at any stage of pregnancy. For the most part these women do well and

TABLE IV

*Showing Functional Grade of 295 Cases of Rheumatic Heart Disease during Pregnancy and Average Age of each Grade. Twenty per cent. of Grade III Cases had Auricular Fibrillation—Average Age 36·8 Years*

Grade.	Total no.	Per cent. of Total.	Average Age.
I	13	4·4	28·4
IIa	126	42·7	29·7
IIb	92	31·2	31·3
III	64	21·7	32·4

are able to go to term successfully and have a natural delivery. It is common to note some deterioration in functional capacity after mid-term, so that a woman classified in the first trimester as Grade I may be Grade IIa by the thirtieth week. Hence the Grade in relation to the duration of gestation is of great importance. The lower in the scale the woman is and the shorter the duration of the pregnancy,

TABLE V

*Showing Relationship between the Functional Grade and the Valvular Lesion*

Grade.	Type of Lesion.	
	Mitral alone per cent.	Mitral and Aortic per cent.
I	80	20
IIa	77	23
IIb	61	39
III	77	23
Deaths	83	17

the worse the outlook. Grade IIb is always a danger signal. Grade III spells disaster and is to be avoided at all costs.

The mild and comparatively innocent groups (Grades I and IIa) comprise a little less than half the total cardiac cases referred to the Clinic. Table IV shows the distribution and average age of a consecutive series of 295 cardiac women examined during pregnancy. It is natural that the mildest cases (Grade I) should be in a minority and that a hospital group should be weighted with the more severe types. Table V, in which the percentage distribution of single or combined valvular defects is arranged for each Grade, indicates that

the degree of deterioration in functional capacity is not directly related to the valvular lesions.

(2) *The Age of the Patient*.—In assessing the immediate prognosis for the individual patient, it is important to bear in mind the natural history of rheumatic heart disease. It is often difficult to gauge the date at which the valvular damage was acquired, but in a rough and ready way the age of the patient provides valuable information analogous to the duration of the rheumatic process. The studies of De Graff and Lingg (1935) demonstrate that the average age at the time of the initial infection is 17 years and the mean duration of life thereafter 15 years. In their experience, cardiac insufficiency first becomes manifest about the age of 28 years, congestive failure about age 30, and death, after a more or less crippled existence, occurs on the average some three years later. Deterioration in myocardial efficiency is at first slow, but the downward slope of the curve quickens in later years as congestive failure approaches, after which the descent to a fatal termination is relatively rapid. As pointed out by Bunim

TABLE VI

*Showing the Influence of a Functional Grade in one Pregnancy on the Functional Grade of a Succeeding Pregnancy*

		Functional Grade in Last Pregnancy (x).			
		I.	IIa.	IIb.	III.
Grade in next Pregnancy (x+1).	I	15 per cent.	1 per cent.	0	0
	IIa	50 "	52 "	0	0
	IIb	25 "	31 "	65 per cent.	14 per cent.
	III	10 "	16 "	35 "	86 "

and Rubricius (1948), the point on the curve at which pregnancy occurs is of great importance in determining the woman's immediate prospects. Gorenberg and McGleary (1941) found that 43 per cent. of rheumatic women over 30 years of age showed evidence of cardiac failure compared with 16 per cent. in the groups under this age. In support of this conclusion we find that on the average the older the patient, the lower the functional Grade during pregnancy (Table IV). Broadly speaking, the younger the patient, the better are her prospects, whereas over age 30 the more probable is the occurrence of serious incapacity. In general the cardiac woman does best to have her family in the early twenties.

(3) *Previous Experience*.—If she has already borne a child, further guidance to the woman's capabilities readily becomes available. Our experience, based on a study of two consecutive pregnancies in 169 women attending the Cardiac Clinic, is that a woman who attains Grade IIb or III in one pregnancy will do so again in the next. This finding is demonstrated in Table VI. Even in the milder Grades (I and IIa) there is a definite downward tendency in a subsequent



pregnancy; for instance, 50 per cent. of those women who were Grade I in the preceding pregnancy were Grade IIa in the next. It is noteworthy that 10 per cent. advanced from Grade I to Grade III in the next pregnancy. In each instance where such a substantial decline was observed twelve years or more elapsed between the two consecutive pregnancies. Similarly, of those women classified as Grade I in one pregnancy and Grade IIb in the next, an interval of at least five years intervened. This observation supports the view already expressed that the age of the patient is of considerable importance in the immediate prognosis, and should be taken into account when considering the patient's cardiac efficiency in the preceding pregnancy.

### CAUSES OF DEATH IN CARDIAC WOMEN

Pregnancy is as a general rule well-borne by the woman with a damaged heart. The death rate in five-year periods has varied between a maximum of 7.5 and 1.8 per cent. (Table I), which implies that with reasonable supervision and selection 98 per cent. of cardiac women may survive pregnancy and labour. In twenty years 46 maternal deaths have occurred—28 (61 per cent.) from congestive heart failure, 7 from bacterial endocarditis (15 per cent.), 6 from acute pulmonary œdema (13 per cent.) and 2 from septic peritonitis (4 per cent.) following Cæsarean section. Of the remaining 3 deaths (7 per cent.) one was attributable to acute rheumatic fever, one to an anæsthetic administered for a perineal repair shortly after delivery and one as a result of an incompatible blood transfusion (hæmoglobinuric nephropathy). No embolic deaths were recorded.

Congestive heart failure is the leading cause of death, and if combined with the fatalities from acute pulmonary œdema amounts to 74 per cent. of the maternal deaths. By urging therapeutic abortion in all Grade IIb and III cases encountered in the first three months, and by continued supervision throughout the remaining months of pregnancy, congestive heart failure can be prevented for the most part. Acute pulmonary œdema, being largely unpredictable in its occurrence, is a formidable risk which all these patients face. Exposed to a hypertensive toxæmia, respiratory infection, undue fatigue or persistent insomnia, particularly if abrupt in onset, the woman with a damaged heart faces much greater risks than her healthier sister. The importance of acute pulmonary œdema as a cause of death amongst cardiac women is likely to increase, as the death rate from congestive failure is now falling and septic deaths, including bacterial endocarditis, can be prevented.

The relation of the fatal cases to delivery is of interest. Table VII, showing the time distribution of the deaths, indicates that two-thirds of the fatalities occur after delivery. Nine of the sixteen deaths from congestive heart failure in the puerperium occurred in the first twenty-four hours, six patients dying within four hours of delivery. All the deaths from congestive failure during pregnancy took place between

the 14th and the 32nd week. None of these patients died in the last eight weeks of pregnancy, when the circulatory load is beginning to lighten and none died during labour. Acute pulmonary œdema, causing death, occurred at the 14th and 39th weeks. One patient died from this cause during labour and three within twenty-four hours of delivery. The suddenness of its onset and its liability to provoke a fatal issue make this complication of mitral valvular disease a real menace to the pregnant woman. It is difficult to forestall and prevent. More work requires to be done on the cause of this form of acute heart failure.

The first twelve hours after delivery are the most critical time for the cardiac woman. Labour itself is relatively benign, only one death occurring at this time. It is difficult to present an adequate explanation for this observation, but it appears that the circulatory readjustments after delivery of the child and expulsion of the placenta place a greater burden on the heart than the muscular efforts of labour. Hoffman and Jeffers (1942) favour the concept that the contractions of the

TABLE VII

*Showing the Distribution of the Deaths: 67 per cent. of the Fatalities occurring in the Puerperium*

Cause of Death.	Before Mid-term.	After Mid-term.	Labour.	Puerperium.
Congestive heart failure	6	6	0	16
Acute pulmonary œdema	1	1	1	3
Bacterial endocarditis	0	0	0	7
Other causes	0	0	0	5
Total . 46	7 (15.2 per cent.)	7 (15.2 per cent.)	1 (2.2 per cent.)	31 (67.4 per cent.)

uterus force blood from the capacious sinuses at the placental site into the general circulation—an autotransfusion—thus overloading the right side of the heart. If this be the explanation, it is surprising that there is not more evidence of maternal distress during labour, when the uterine contractions are maximal. It may be that the cardiac woman, handicapped by congestive failure in greater or less degree at the time of her confinement, makes a less rapid readjustment of the excess blood volume in consequence of temporary renal insufficiency. The fact that deaths are so prevalent in the early days of the puerperium suggests that energetic measures for the prevention of congestive failure should be brought into use even before the onset of labour, and continued carefully over the succeeding days.

#### THE OBJECTS OF ANTE-NATAL SUPERVISION

The main intention in the supervision of these women is the adoption of measures to prevent the development of congestive heart failure—the commonest cause of death. If further reductions in the mortality rate from organic heart disease are to be achieved in the future, the cardiologist and obstetrician must have the opportunity to see and

grade all cardiac women within the first four months, or earlier. Pregnancy should be terminated in the great majority of patients classified as Grade IIb and in all in Grade III by the sixteenth week, after which interruption becomes a major procedure associated with considerable risk for the cardiac patient. Early interruption should also be practised in those women who have been classified as Grade III in a previous pregnancy. By this means serious deterioration about the middle or end of pregnancy and death shortly after delivery can be avoided. This aspect of the successful prevention of maternal deaths by early therapeutic abortion must receive wider publicity. We will then be spared the tragedy of maternal deaths through neglect of simple measures appropriate to the first trimester.

The second step in prevention of congestive heart failure is full use of the admirable facilities available for in-patient treatment in the wards of the ante-natal department. Any patient who can be classified as Grade IIb should be put to bed in hospital and with few exceptions kept there until term. None admitted in Grade III and few in Grade IIb should be allowed to return to their homes. When this advice is disregarded, all too often the patient is brought back to hospital some weeks later more gravely ill than before. For the alleviation of circulatory distress, the up-grading of functional capacity and the prevention of serious congestive failure, there is for these women, in whom danger threatens, no remedy superior to prolonged rest in bed with adequate sleep.

The third step in the prevention of the development of congestive failure during pregnancy is continued attention to the woman's general health. She should visit the clinic every two to three weeks, with a view to assessment of her functional grade and with the object of ensuring that anæmia and insomnia are adequately corrected. Upper respiratory tract infections are of the greatest danger and more liable to precipitate congestive failure than labour itself. Colds, catarrh, bronchitis, asthmatic attacks, should be taken seriously, the patient put to bed and appropriate medical measures commenced at once.

### IS CÆSAREAN SECTION JUSTIFIED?

The most difficult cases are those who are found in Grade III about mid-term. As a general rule these women, having had no preceding ante-natal supervision of the heart, will soon show some improvement with adequate bed-rest and medical care. The first consideration is energetic treatment for the congestive failure. This implies days or weeks of strict medical measures—rest, hypnotics, digitalis, mercurials and a salt-free diet—before a decision is taken on the next step. If a good response is obtained, so that the patient may be reclassified as Grade IIa or IIb, the justification for obstetrical interference is slight. Strict measures and absolute confinement to bed must be maintained for the remainder of the pregnancy in the hope that a natural vaginal delivery may be safely accomplished.

If, on the other hand, energetic medical treatment fails to abolish

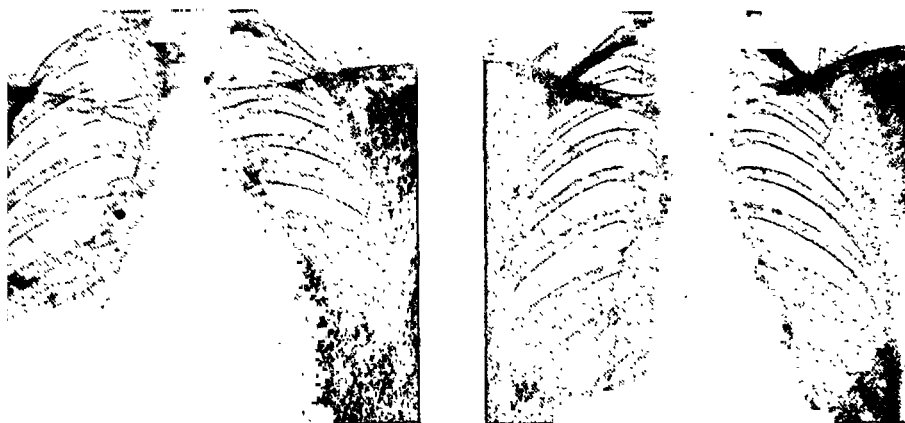


FIG. 1.—Showing the effect of pregnancy on the size and shape of the heart. “A” is the frontal view taken one month before delivery. “B” is the same heart eighteen months later.

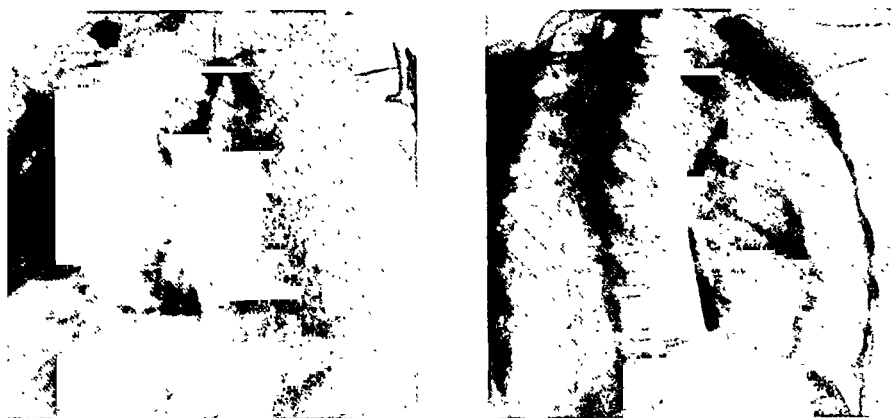


FIG. 2.—Showing the influence of pregnancy on the shape of the heart as demonstrated by the right oblique view. The radiograms are from the same patient as those in Fig. 1 and were photographed at the same time. “A” shows the effect of elevation of the diaphragm one month before term. The left auricle displaces backwards the barium-filled œsophagus. “B,” recorded eighteen months after delivery, shows that the heart has regained its position, with the descent of the diaphragm and that the left auricle is no longer distended. This particular patient was suspected during pregnancy to suffer from mitral stenosis on account of a rheumatic history, a mitral systolic murmur and congestive heart failure, on which account a Cæsarean section after full digitalisation was performed shortly before term. Examined eighteen months after delivery, no conclusive sign of rheumatic heart disease could be recognised.



completely the signs of congestive failure and the patient remains orthopnœic and easily distressed, there is a natural urge to empty the uterus. The prognosis both for mother and child is grave if the pregnancy is allowed to proceed and probably even more grave if surgical intervention is undertaken in the presence of congestive failure. McIlroy and Rendel (1931), discussing the problem of the artificial termination of pregnancy in such circumstances, advise adherence to their working rule—"when in doubt don't interfere." Labour in tragic circumstances is often made easier by nature herself. The present-day tendency is to discourage operative interference (Hamilton, 1937) for, as Hamilton and Kellogg (1928) have pointed out, "there will never be a really satisfactory method of delivering a woman in heart failure."

In considering the question of hysterotomy or Cæsarean section in the presence of the more serious grades of heart failure, it must be admitted that the effect of a major operative procedure on circulatory dynamics is most obscure. With modern anæsthesia and skilled surgical technique there is no reason to suppose that extra work is performed by the heart during a laparotomy. It has therefore been claimed that an abdominal delivery is less strenuous than a natural confinement and less exhausting when the cardiac reserve is low. The fact remains that the strain of the few days immediately following operation is greater than after a natural vaginal delivery. Shock is more profound after surgery, the heart faster, the pulse pressure lower, the discomfort greater, embolic pulmonary phenomena more frequent and the risk of infection enhanced. The inadequate ventilation of the lung bases, usual after a major abdominal procedure, coupled with the pulmonary congestion accompanying the cardiac damage, predispose to atelectasis and a reduced resistance to infection. In turn the adverse influence of respiratory tract infections on the right side of the heart is well known. Although the patient may weather the laparotomy, an advance in the degree of congestive failure within a few days of delivery is usual and death common. Snyder (1938) found a decrease of 41 per cent. in cardiac output directly after surgical operations while the patients were still under the anæsthetic. One to four days commonly elapsed before the output of the heart returned to normal. This suggests a degree of myocardial depression sufficient to account for the poor response so commonly recorded in the presence of heart failure.

Facts and impressions are gradually accumulating to support the view that Cæsarean section in late pregnancy is undesirable. After the thirty-sixth week the burden on the heart begins gradually to decrease, the blood volume, cardiac output and velocity of blood flow diminishing steadily with a consequent diminution of cardiac work. It is unwise to operate a month or more before term when the circulatory burden is maximum. Medical measures should be maintained until delivery. McIlroy and Rendel (1931) adopted the policy of operating only after labour had been in progress for some hours.

Many of their patients earmarked for Cæsarean section had spontaneous deliveries without untoward consequences. In severe cases, if labour is likely to be protracted and difficult owing to cervical rigidity, then there may be no alternative to Cæsarean section without trial labour.

Statistical studies of mortality rates are unsatisfactory as exactly comparable groups are difficult to obtain. Furthermore, the selection of cardiac patients for abdominal deliveries varies greatly in different teaching centres. Whereas 27 per cent. of cardiac women are delivered by this means in Liverpool, it is employed only in 5·5 per cent. in

TABLE VIII

*Showing Incidence of Casarean Section amongst Cardiac Women and Mortality Rate following Section in Different Centres over Twenty Years*

Centre.	No. of Cardiac Cases.	Cæsarean Sections.		Deaths.	
		No.	Per cent.	No.	Per cent.
Edinburgh . . .	1100	124	11·3	11	8·8
Glasgow . . .	2183	185	8·4	18	9·7
Liverpool . . .	730	197	27·0	7	3·5
Manchester . . .	1401	76	5·5	6	7·8

Manchester. Glasgow and Edinburgh are mid-way between these extremes (Table VIII). The death rate varies between a minimum of 3·5 per cent. at Liverpool to a maximum of 9·7 per cent. in Glasgow. The explanation must be that in the Liverpool series, where frequently the main indication for the operation was combined sterilisation with delivery, the proportion of gravely ill cardiac patients is less than in Glasgow or the other centres. In Manchester, where Cæsarean section

TABLE IX

*Showing Percentage of Cardiac Cases Delivered by Casarean Section in Different Centres over the Past Twenty Years Divided in four-year Periods*

Centre.	1928-31.	1932-35.	1936-39.	1940-43.	1944-47.
Edinburgh . . .	14·9	11·0	9·9	13·0	9·8
Glasgow . . .	14·3	9·0	9·2	6·0	4·7
Liverpool . . .	14·2	29·4	41·1	31·0	22·7
Manchester . . .	4·6	5·3	8·5	5·0	4·4

is used very little, as many of the bad risk cases are now-a-days picked out early and the pregnancy terminated, a common practice is to rupture the membranes and allow the cardiac woman to have a normal labour. Analysed in four-year periods, Table IX shows that the frequency with which Cæsarean section has been performed at the four centres during the past twenty years has shown no particular tendency to decrease, with the exception of Glasgow, in which abdominal delivery was formerly practised three times as frequently as at present. From the information which we have collected regarding current practice elsewhere, and from our Edinburgh experience, it appears that within the last two or three years the frequency with which

Cæsarean section is now being performed is showing a steady decrease. Sufficient time has not elapsed to present corresponding figures.

Just as hospitals differ in their outlook, obstetricians in their performance, anæsthetists in their skill and cardiologists in their ability to grade and classify patients, so comparative statistics may mislead. Nevertheless, interesting studies have been made. Mendelson (1944) observed a series of Grade IIb and III cardiacs, who experienced a mortality rate of 9·5 per cent. following abdominal delivery, as compared with no fatalities following natural birth (Table X). The vaginal group included 34 Grade III cases, with auricular fibrillation. We do not claim that the figures as presented are statistically significant. At the most they suggest that the mortality rate after Cæsarean section is at least twice as high as after pelvic delivery. Stromme and Kuder (1946) from their experience of the severer types of rheumatic heart disease in pregnancy report an increased incidence of forceps deliveries with a reduction in the frequency of Cæsarean section from 4·1 to

TABLE X  
*Showing Mortality Rates following (a) Cæsarean Section and  
(b) Pelvic Delivery in Different Centres*

Source.	Cæsarean Section.			Pelvic Delivery.		
	Total.	Deaths.		Total.	Deaths.	
		No.	Per cent.		No.	Per cent.
This Series (1949) } Grade IIb and	81	10	12·4	176	12	6·8
Mendelson (1944) } III cases only	21	2	9·5	101	0	0
Gorenberg and McGleary (1941)	29	4	13·8	315	6	1·9
Hamilton and Thomson (1941)	180	15	8·3	706	14	2·0

1·6 per cent. Bunim and Rubricius (1948) go so far as to state that the presence of rheumatic heart disease is no longer acceptable as an indication for Cæsarean section, and support for this is found in the work of Gorenberg (1943) who claims that by hospitalising every woman, showing a significant decrease in cardiac reserve, for the remainder of her pregnancy and by ordering increased bed-rest for every cardiac patient from the sixth month onwards, the incidence of Grade IIb and III cases was reduced from 22 to 0·5 per cent. Surgical intervention was considered contra-indicated and labour was allowed to occur spontaneously. By adopting these methods his mortality rate in cardiac patients dropped from 3·5 to 0·6 per cent. This author concludes that by more intensive ante-natal care and absolute bed-rest, practically every pregnancy encountered in the presence of organic heart disease can be brought to a successful spontaneous termination. Cæsarean section was avoided by better care.

If it proves to be true, as the present trend of thought suggests, that even in grave cardiac distress pelvic delivery is safer than abdominal, then, with other methods available, the necessity for sterilisation cannot now be held to justify Cæsarean section amongst



cardiac women. A considered conservatism with an abandonment of the supposed advantages of hasty surgery is the leading trend in obstetrical care of the cardiac patient at the present time. The justification for Cæsarean section grows less and less.

### THE HEART AFTER PREGNANCY

While our knowledge of the immediate influence of pregnancy on the damaged heart is substantial, of the ultimate effects we can speak with less certainty. To ascertain if pregnancy or repeated pregnancies in any way alter the expected duration of life in the woman already handicapped by organic heart disease is a more formidable problem than might appear at first sight.

It was thought that a "follow-up" examination of the women who attended the Cardiac Clinic during the ten-year period 1937 to 1946 might yield information of value. During this decade there had been over 500 pregnancies in 385 cardiac women. Patients dying during pregnancy or in the puerperium were excluded from the survey

TABLE XI

*Showing Incidence and Types of Heart Disease on "Follow-up" Examination of 352 Women regarded as Cardiac Subjects during Pregnancy*

Etiology.	Incidence per cent.
Rheumatic heart disease . . . . .	85.0
Negative . . . . .	10.2
Congenital . . . . .	2.6
Miscellaneous, thyrotoxic, specific, hypertensive . . . . .	2.2

and over a dozen unmarried women were considered unsuitable for follow-up purposes.

This leaves 365 patients available for study. Of these 352 (96 per cent.) were traced, nearly all of whom were examined by one of us. Information regarding a few now resident at a considerable distance was obtained from the local practitioners. Only 13 women (4 per cent.) temporarily resident in Edinburgh during the war years, whose present whereabouts is unknown, remain untraced. There is no reason to believe that they had died in the interval since they last attended the hospital.

### FICTITIOUS HEART DISEASE

Of the 352 women, observed at dates varying from one to ten years after their last attendance at the Cardiac Ante-Natal Clinic, 37 (10.5 per cent.) had no detectable organic lesion. The remaining 315 presented conclusive evidence of organic heart disease, nearly all of which was rheumatic in origin (Table XI). It was of considerable interest to discover that 1 in 10 of the so-called cardiac women, when re-examined some years after the pregnancy in which their heart had been suspect, had in fact no organic heart lesion as judged by clinical, radiological and electrocardiographic examinations. This

does not imply slackness in diagnosis during pregnancy, but emphasises the great difficulty in establishing the presence of a valvular flaw when the heart is overtaxed for some other reason. We can therefore confirm Gammeltoft's (1928) suspicions that the circulatory adjustments in a healthy pregnant woman could so mimic heart disease as to cause considerable confusion.

When it is appreciated that in her circulatory functions a healthy pregnant woman at rest behaves similarly to a non-pregnant woman engaged in moderate work (Widlund, 1945), it can be understood how breathlessness on effort may be noted after mid-term. Some healthy women during pregnancy are a trifle orthopnoic and even develop scattered râles at the lung bases; a few may even show a more complete picture of congestive failure with œdema of the ankles and occasionally of the lumbar region, the latter being more commonly found in the presence of hydramnios. Reference has already been made to the importance of accepting only well-recognised signs as evidence of organic heart disease during pregnancy.

TABLE XII

*Showing Distribution of 37 (10 per cent.) Cases found to have no Organic Heart Disease on "Follow-up" Examination*

Clinical Findings during Pregnancy.	No.	Rheumatic History.
Mitral systolic murmur . . . .	17	8
C.H.F.,* IIb and III . . . .	7	6
Anæmia . . . . .	5	3
Extrasystoles . . . . .	2	1
Edema due to toxæmia . . . .	6	1

\* Congestive heart failure.

Our 37 negative cases have been examined in greater detail, as shown in Table XII. The largest number (17 cases) had been classified as cardiac patients on account of a mitral systolic murmur, with some slight limitation in activity (Grade IIa). A rheumatic history in half the patients added to the difficulties. Anæmia, in five women with a marked functional disability (Grade IIb) particularly with a rheumatic history, was the cause of much confusion, and six patients suffering from pre-eclamptic toxæmia had been labelled cardiac disease either because of left ventricular failure or of suspected associated heart disease.

There remains a group of 7 women. All showed signs of congestive heart failure (Grade III) during pregnancy and were then severely handicapped. On follow-up examination some years later they were fit and well, leading active lives. No conclusive sign of organic heart disease could be found on physical examination. During pregnancy these women had required rest in bed for varying periods before term. By this means the œdema cleared in four, and in the remaining three digitalis was required in addition. None had shown evidence of anæmia, fever, kidney disease or toxæmia of pregnancy, and as far as can be ascertained their diets were adequate and their nutrition

satisfactory. The condition of two of these women was considered serious enough to warrant Cæsarean section. Examined respectively ten years and one year later, no conclusive evidence of organic heart disease could be recognised.

The explanation for this phenomenon no doubt lies in a combination of a number of factors. All the patients were over 30 years of age, six of the seven gave a history of rheumatic fever, though none had residual evidence of endocardial damage, by which rheumatic heart disease is commonly recognised clinically. This suggests that the after-effects of cardiac rheumatism may be confined to the myocardium. Without autopsy studies it is not possible to substantiate such a proposition. The alternative suggestion, that the healthy heart, as a result of incomplete adaptation to the circulatory burden of pregnancy, may fail temporarily when no permanent organic cardiac flaw exists, is less convincing, and we consider it probable that rheumatic myocarditis, unaccompanied by a valvular flaw, is a distinct but uncommon clinical entity.

TABLE XIII

*Showing the Functional Grade of 254 Cases of Rheumatic Heart Disease some Years after Pregnancy and the Average Age of each Grade. Compare with Table IV*

Grade.	Total No.	Per cent. of Total.	Average Age.
I	17	6	31
IIa	149	59	35
IIb	69	27	37
III	19	8	41

To summarise, we find, from examinations made some years after delivery, that during pregnancy there are a few conditions which may closely resemble organic heart disease. The mitral systolic murmur is often considered organic in nature when no flaw exists. Anæmia is a cause of symptoms and signs resembling heart disease and the hypertensive toxæmias may on occasions mimic permanent organic damage. Finally, there is a small group of cases where it would appear that the heart actually fails during pregnancy when, as far as can be made out on subsequent clinical examination, no permanent organic cardiac lesion can be demonstrated, though a rheumatic myocarditis in the absence of a valvular flaw is difficult to exclude.

#### FATE OF SURVIVORS

Of the 295 patients, 41 died between one and ten years after the observed pregnancy. The remaining 254 women were in varying degrees of health. On the basis of their circulatory efficiency it was possible to re-classify them using the same four grades employed during pregnancy, as shown in Table XIII. These figures demonstrate that age and functional capacity bear a close relationship. As in pregnancy, so also some years later—the older the patient, the more likely is she to be severely handicapped.

If an attempt is made to assess the state of health of cardiac women in the years succeeding pregnancy as compared with their state during pregnancy, it is found that those who were Grade I during pregnancy keep in very good health thereafter. Nearly all the patients classified as Grade IIa during pregnancy maintained this degree of efficiency for many years. Less than 5 per cent. of our series developed congestive heart failure and an equally small number had died.

On the other hand, those who were more severely handicapped (the Grade IIb cases) did not do so well. About half returned to an active life which they maintained for only a few years. The majority were severely handicapped and were bordering on congestive heart failure. More than 10 per cent. had died.

Of those who had shown congestive heart failure during pregnancy (the Grade III cases) roughly one third had died cardiac deaths within a few years, one third remained severely handicapped and one third had improved to such an extent that they could be reclassified as Grade IIa. There were some remarkable recoveries in this group. One woman who had been in severe congestive failure during pregnancy, after which she had been sterilised, was two years later completely symptomless, doing normal housework and in addition outside work. Several cases seen between six and ten years following congestive heart failure during pregnancy were still well compensated and leading active lives.

On the basis of this follow-up examination, it appears that pregnancy is capable of inducing congestive heart failure in a woman roughly five to seven years before it is due to appear in the normal course of events. It is, however, difficult to determine with any accuracy the influence of pregnancy or repeated pregnancies on the ultimate development of congestive heart failure, or in other words, whether pregnancy hastens the fatal termination in the progressive deterioration inseparable from rheumatic heart disease.

If child-bearing had a distinctly unfavourable effect on the ultimate outcome, it would be expected that, amongst women who had reached the child-bearing age, death might well occur at a younger age in the parous as compared with the nulliparous women. Gilchrist and Murray Lyon (1933) found the age at death similar in the two groups. Boyer and Nadas (1944), from clinical and pathological studies, concluded that pregnancy had no adverse influence on the course of rheumatic heart disease. More recently Cohn and Lingg (1948), in an exhaustive study involving 1500 cases of cardiac rheumatism followed through the child-bearing age to death, concluded that there was no reason to believe that child-bearing had an adverse influence on the course of the disease.

If a comparison is made of the average age at onset of severe congestive heart failure in rheumatic heart disease amongst patients admitted to the general medical wards of this hospital, but excluding patients under 20 years of age, it is found that there is no significant age difference between the sexes or between nulliparous or parous women (Table XIV). Congestive heart failure in rheumatic heart disease is

commonly encountered about 41 years of age. It does not occur at an appreciably earlier age in parous as compared with nulliparous women.

If pregnancy had an adverse effect on the course of rheumatic heart disease, it is reasonable to suppose that repeated pregnancies would have an even worse effect. Preliminary statistical analysis does not lend support to this contention. By using the death rate as a basis for comparison, it is found that deaths occur in the same proportion in cardiac women who have had one, two or multiple pregnancies. It therefore appears that the number of pregnancies does not influence the death rate. Furthermore, by using the functional grades observed during and after pregnancy as a basis for comparison, it is found that the course of the disease, as estimated by the rate at which the downward trend in grade occurs over the years, is not affected by the number of pregnancies, the curve being the same in each of the groups. From these angles it therefore appears that on the average the rate of progression of rheumatic heart disease is much the same in all women, irrespective of the number of pregnancies.

TABLE XIV

*Showing the Average Age of Occurrence of Congestive Heart Failure of Rheumatic Origin in Different Groups observed in a General Hospital*

	Number.	Average Age.
Men . . . . .	71	41.8 years
Nulliparous women . . . .	65	42.3 "
Parous women . . . . .	87	40.6 "

We conclude that there is nothing to suggest that the heart is damaged by child bearing or that the course of the prolonged rheumatic process is thereby accelerated. Pregnancy can be regarded as a temporary complication of heart disease, inducing serious inroads on the cardiac reserve. On occasions the heart is overwhelmed, but provided the demands are met, it appears that no permanent damage is sustained and that the cardiac condition reverts to its former state. A patient with heart disease, having overcome the dangers of pregnancy, may survive many years and ultimately die no younger than had she never borne a child.

#### ACKNOWLEDGMENTS

To our colleagues in the Obstetrical Department of the Royal Infirmary we express our warmest thanks for their co-operation and for all the facilities extended to us during recent years. We also acknowledge the considerable help which we have had from the Obstetrical Registrars in Glasgow, Manchester and Liverpool, Dr W. F. Harper, Dr R. Newton and Dr L. W. Cox, who have searched their records and placed at our disposal the necessary figures from which we have constructed the corresponding statistical analyses.

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#### DISCUSSION

*Dr Hewitt* (Glasgow) emphasised that the most important point was the decision in the early months as to whether or not pregnancy should be allowed to continue. If the decision to allow the pregnancy to continue was correct, then the management thereafter was comparatively straightforward and it mattered relatively little which mode of delivery was adopted. In his own experience, he found that he was performing Cæsarean Section less and less frequently in cases of cardiac disease. The operation was never justified for the sake of carrying out sterilisation. This procedure could be performed more safely at a later date. In some cases the tenth day of the puerperium was a convenient time. *Dr Hewitt* also suggested that, in some cases wrongly diagnosed as cardiac disease, the real cause of the symptoms was an infection of the urinary tract.

*Dr Miller* (Edinburgh) stressed the importance of full co-operation with the cardiologist in the management of patients with cardiac disease associated with pregnancy, but disagreed with *Dr Hewitt* as to the optimum time for sterilisation. He thought that a period of recovery of some three months should be allowed after confinement before the patient was subjected to an abdominal operation.

*Dr Turner* (Edinburgh) discussed the problems of diagnosis with special reference to œdema and breathlessness, and stressed the importance of X-ray

screening in differential diagnosis. He pointed out the dangers of child-rearing as distinct from child-bearing and considered that no woman with rheumatic cardiac disease should have more than three pregnancies and, in many cases, this number should be reduced, but naturally various factors would influence the decision.

*Dr de Soldenhoff* (Irvine) agreed that the decision for therapeutic abortion or continuation of pregnancy should be made very early in pregnancy and also agreed that patients with cardiac disease do well in vaginal delivery. He considered that complete bed rest in hospital was the primary essential in treatment, and the period of hospitalisation would vary with the grouping of the individual case. In all cases he advocated hospitalisation for a period immediately before delivery and recommended a three months delay in carrying out sterilisation following delivery.

*Dr Fraser* (Perth) regretted that such a large series of cases had not also been analysed from the obstetric point of view. He drew attention to the remarkably short labours often experienced by patients with cardiac disease but could put forward no satisfactory explanation. He suggested that an analysis of maternal deaths in relation to type of anæsthesia employed might provide an explanation of some post-partum deaths and point to the value of local anæsthesia in forceps delivery or Cæsarean Section. Dr Fraser expressed the opinion that sterilisation would not be justified if deterioration of the patient was, in fact, due to age alone and was not accelerated by repeated pregnancy. On the other hand, if deterioration did occur, would it not be wise to space pregnancies to permit adequate recovery in the intervals?

The President (*Dr Fahmy*) found it difficult to explain the underlying cause of death within 48 hours of vaginal delivery or 4 to 5 days following Cæsarean Section. With regard to induction of premature labour, he thought this to be both unwise and unnecessary, for it was much safer for the mother in cardiac cases to commence labour spontaneously; prolonged labour which frequently followed premature induction was a very serious handicap. In the last month of pregnancy cardiac cases frequently showed improvement and most clinicians had recognised this fact—this might be related to the lessened cardiac output which appeared to occur at this time, and to the fact that the blood volume did not increase during the last month. The patient had a chance to become stabilised prior to the onset of labour. He deprecated the use of forceps as a routine as soon as the cervix was dilated for that procedure frequently meant a mid-forceps operation. If the heart showed no undue strain, then spontaneous delivery should be allowed to occur, even in primigravidæ, with or without an episiotomy incision. Forceps should be applied when necessary, but not as a routine. Dr Fahmy referred to the dangerous association of toxæmia and cardiac disease and pointed out the risk of cardiac failure even in cases of clinically mild toxæmia. He recalled two cases of sudden death in young patients exhibiting extra-systoles in the absence of recognisable valvular disease, but was at a loss to account for the underlying pathology which caused the deaths.

*Dr Somerville* (Bonnyrigg), together with Drs Hewitt, Miller and Fahmy found it difficult to correlate the views of Dr Gilchrist and Dr Haig with regard to the deterioration of cardiac patients as a result of pregnancy and increasing age, and requested clarification on this point.

In reply, *Dr Gilchrist* repeated the contention that a succession of pregnancies does not necessarily shorten the ultimate course of rheumatic heart disease provided the patient survives the pregnancy.

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(Jeffcoate) on which normal uterine action, in labour, must largely depend :—

- (1) Growth and development of the uterus during pregnancy.
- (2) The reason for the onset of labour.
- (3) Uterine polarity and cervical dilatation.

(1) *Growth and Development of the Uterus during pregnancy.*—This is influenced mainly by the two hormones œstrin and progesterin. They are thought to be responsible for increased vascularity, hypertrophy of muscle with control of its contractions, sensitivity and tone. It has been shown that as pregnancy advances, the amount of œstrogenic hormone in the circulation increases but until the later weeks the major part is in a combined and inactive form. Shortly before labour it becomes activated and free to exert its full biological effect. The uterine sensitivity increases as the œstrogenic hormone becomes more and more dominant. To a lesser extent the growth of the uterus is controlled by the increasing bulk of the uterine contents and by an adequate supply of ordinary nutritive agents, organic or inorganic.

(2) *The Reason for the Onset of Labour.*—It is believed that œstrin is the main sensitising factor of the human uterus and when adequate priming has occurred, any further stimulus, *e.g.*, pressure of the presenting part on the lower segment or some emotional disturbance, may be enough to establish the onset of labour. Some hold that the œstrogenic hormone provokes the onset of expulsive uterine contractions while others say that the growth response is limited by this hormone and when further uterine enlargement is prevented by increasing œstrin, labour commences. Kneer suggests that œstrin withdrawal, as in menstruation, may be a factor in initiating labour. Hoffman enumerates the views that œstrin may stimulate the posterior pituitary lobe to secrete its oxytocic principle or may render the uterus sensitive to the posterior pituitary-like hormone. The view that progesterin withdrawal is at least partly responsible for the onset of labour is based on evidence that this hormone exerts an inhibitory effect on uterine muscle.

(3) *Uterine Polarity and Cervical Dilatation.*—This mechanism must surely be influenced by several factors. There may, for example, be some sort of balance between the adrenergic effects of nerve stimuli and the cholinergic effects of œstrogens. Goerttler and Kreis suggest that the longitudinal muscle fibres of the upper segment and the circular ones of the lower segment act as single fibres arranged with a straight upper stem and a closely coiled root. When the upper part of the fibre contracts, the spiral or lower part is uncoiled and straightened out and this automatically results in decreased resistance and dilatation of the lower segment. Normal retraction of the cervix over the presenting part is accelerated by an absence of disproportion, by a normality of position—indeed by all those factors which go to make an accuracy of fit between presenting part and lower uterine segment. It is difficult to be dogmatic as to why this should be so but the idea

that an accurately fitting presenting part may more adequately stimulate the nerve filaments in the lower segment and adjacent tissues would seem to be sound. It is realised that, in the majority of cases, the frequency and intensity of uterine contractions are influenced profoundly by the pressure of the presenting part on the lower segment. Obviously, therefore, anomalies in cervical dilatation are associated with disordered uterine contractions and in those cases where labour is prolonged it may be impossible to say with certainty whether the inertia of the upper segment is the cause or the result of slow cervical dilatation or whether both processes are at fault.

In this paper I propose to discuss two forms of inefficient uterine action:—(1) Constriction ring dystocia, (2) Inertia with reference to the hypotonic and hypertonic types.

*Ætiology.*—Those two conditions have in their ætiology and treatment much in common. There is a general consensus of opinion that primigravidæ are more often affected than multiparæ and that freedom from difficulty in subsequent labours indicates the temporary nature of those conditions as they may affect the uterus or its innervation. There agreement stops. Malposition, malpresentation, deformed or contracted pelvis and increased age are said to predispose. It is probable that a lack of normal stimulus to the cervix and pelvic plexus may, in such cases, affect the upper segment by the nervous route. Rupture of the membranes, before or early in labour, is advanced by some as a possible factor. There is also the view that malfunction in the action of those endocrine glands which should, ideally, steadily lead to progressive and painless childbirth, may be responsible for inadequate uterine action. Such malfunction is probably itself produced by emotional disturbance.

Whereas all the above may play their part in producing constriction ring dystocia or inertia, there are other considerations which appear to me to be more closely related to one or other of the disordered actions under discussion. For example, we know that drugs, given at the wrong time or in improper dosage, may cause a constriction ring; so too, on occasion, may extra- or intra-uterine manipulation. Again, and this is more closely related to constriction ring than to inertia, references are found in the literature showing that not infrequently the uterus manifests asymmetrical contractions, tonus states and other conditions known as "obliquity of the uterus," "asymmetry of the uterus in early pregnancy" and "placental site paralysis." Rudolph believes that this is due to the fact that the uterus, anatomically and physiologically, is fundamentally a bilateral organ and in abnormal states may contract arrhythmically or asymmetrically. He has presented an argument supporting the theory that the uterus possesses a co-ordinating mechanism regulating the motor activity, not only of its sagittal halves, but also of its transverse segments. This mechanism may be upset by a block between the two halves—a slow conduction in one half or an absence or functional defect of the

mechanism on one side, would cause an absence of contraction in one half and a condition simulating uterine obliquity.

If we turn now to inertia, we find that extensive damage done to the uterine wall, as in accidental hæmorrhage, may prevent efficient contraction of uterine muscle. Fibroids, scars and maldevelopment are not, in themselves, adequate cause. Further, we have seen that the œstrogenic principles, circulating during pregnancy, are in an inactive state. This suggests the existence of some mechanism which is protective in so far as the hormone is prevented from sensitising the uterus prematurely. If such a conception be true, it may be that some cases of inertia are due to a persistence of this mechanism and any œstrogenic hormone given will be inactivated and rendered useless. Williams, in an article on the Dystocia Dystrophia syndrome, describes the clinical picture of a primigravida late in the reproductive era and in whom fertility is low. Such patients tend to be short and obese with male characteristics. The menstrual history is irregular, the pelvis small and deformed, the vagina narrow and the pelvic floor rigid. There is a high risk of pre-eclampsia, pregnancy may be prolonged, the membranes may rupture early, the contractions are weak and cervical dilatation is slow. The head may fail to rotate anteriorly and interference and lacerations are the rule. The risk for the child is increased. The patients will, of course, by no means show all of those features and the inertia may be associated only with malposition or with endocrine dysfunction of which the adiposity and masculinity are other manifestations.

Hydramnios and multiple pregnancy are said to be associated with inertia. I feel strongly that this is not so, as the premature and short labours which characterise both conditions do not suggest any loss of tone. The third stage, bleeding, which may follow a twin delivery is due not to inertia but rather to the mechanical difficulty in separating and expelling the larger placenta.

At this stage it is impossible, unfortunately, to avoid reference to the nerve supply of the uterus. I say unfortunately because the views I express may well be the target for a bombardment of contradiction. There is the consolation, however, and it is a considerable one, that my view on this matter may be just as good as that of anyone else!

Although there is nowadays the opinion that the parasympathetic has little or nothing to do with uterine activity, I prefer to think that this is not so and that the uterus is served by the sympathetic and parasympathetic systems. The sympathetic is derived from the 10th, 11th and 12th thoracic nerves through the hypogastric plexus or presacral nerve running to the pelvic, utero-vaginal, cervical or Frankenhauser plexus, which may also receive fibres directly from the lower lumbar and sacral sympathetic nerve trunks. Joining this plexus is the parasympathetic supply through the 2nd, 3rd and 4th sacral nerves—the *nervi erigentes*.

It has been said that the parasympathetic is motor to the muscles of expulsion—the longitudinal fibres of the upper segment, while the

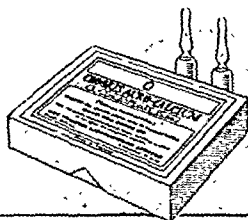
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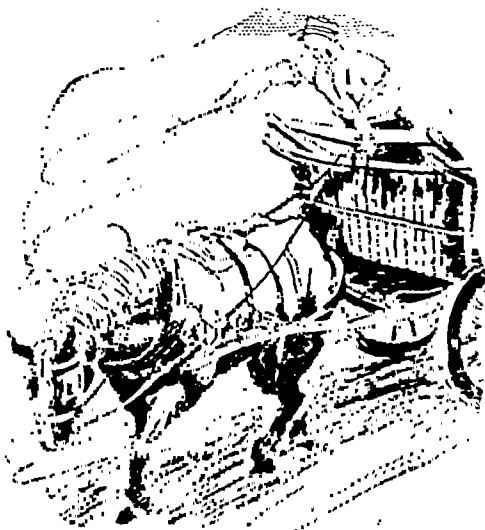
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sympathetic is motor to the muscles which inhibit expulsion—the circular fibres at the internal os. There appears to be some evidence for this but the division of the uterine wall into longitudinal and circular coats is obviously incomplete when no account is taken of the oblique middle layer, the thickest layer of all. Likewise the variable response which the uterus gives to stimulation of the sympathetic, under different conditions, invalidates any general conclusion as to the function of that part of the autonomic system. The belief that the sympathetic contains almost the entire sensory nerve supply of the uterus is now also a matter for controversy.

Elkin has recorded that women who have suffered fractures or new growths of the spine may yet have a normal labour and many of us can vouch for such a labour following presacral neurectomy. It is assumed, therefore, that automatic contractions of the uterus must be under the control of a local centre—the great cervical ganglion assisted by smaller ganglia distributed throughout the uterine wall. Such local nerve centres may be responsible for automatic contractions of the expulsive muscle if the polarity of the uterus, the synergistic action of the upper and lower segments, is hindered by some fault in the autonomic system.

Contraction of the upper segment inhibits the action of the lower segment, thus allowing dilatation of the os whereby uterine polarity is established. It follows, therefore, that an integrity of action of both sympathetic and parasympathetic is essential for the normal mechanism of labour. How may this integrity of action be interfered with? The answer—in several ways for, as we have seen, about the ætiology there is much controversy, but I would ask you to consider for a moment the possibility that the harmony of uterine action may be shattered by the discord of fear. I believe this to be the most important ætiological factor associated with inco-ordinate uterine action, more especially perhaps in relation to uterine inertia.

Many of us have seen the patient, usually a primigravida, with normal presentation and position, the head deeply engaged in the pelvis for a week or two before labour starts. An easy labour is anticipated. Instead, the patient has an inertia, labour may drag on for several days and finish with an unpleasant and difficult instrumental delivery. Subsequent questioning elicits the information that the patient, throughout her pregnancy, has been terrified of the unknown ordeal ahead and, keeping this fear to herself, has lived for months in a state of suppressed anxiety. Some will ask, "But what about the inertia which may affect the carefree, placid patient, apparently happy in her pregnancy?" I would reply that there is nothing more difficult to assess than the mental attitude of the woman towards her forthcoming labour. It is often the patient, casual and outwardly unperturbed by what lies ahead, determined not to give way to her fears or to confess to them, who becomes the victim of inertia.

As Read says, the influence of fear being conveyed through the sympathetic nervous system, inhibits the pelvic autonomic. As a

result of this the neuro-muscular harmony of labour in the presence of fear is disturbed in a manner exactly similar to that produced by pain. Resistance is produced in the lower uterine segment and cervix and although the pelvic autonomic may cease to influence labour, the inherent ability of the upper segment to continue its expulsive efforts increases the tension. Read believes it is possible therefore to appreciate the influence of the emotions upon labour, both directly through their motor responses and indirectly through the endocrine secretions.

### I. CONSTRICTION RING DYSTOCIA

Herman Johnson, as recently as 1946, includes retraction and constriction rings in the term "Contraction Ring" irrespective of whether the ring occurs in obstructed or unobstructed labour. This, I would submit, is wrong. A constriction ring is not a retraction or Bandl's ring which is situated at the junction of the upper and lower segments, ascends in obstructed labour and is accompanied by thinning and maybe rupture of the lower segment. A constriction ring does not rise, remains fixed to the foetus and is not accompanied by spontaneous uterine rupture. There are three main types of uterine ring formation :—

(1) The physiological retraction ring which is normal and occurs in the form of a ring or ridge at the junction of the upper and lower segments.

(2) The pathological retraction ring—Bandl's ring—which occurs in obstructed labour or mechanical dystocia and is the result rather than the cause of the dystocia. This is merely an exaggeration of the normal physiological retraction ring.

(3) Constriction ring—definitely abnormal. This is an annular contraction of the uterus which may occur, theoretically, at any level of the uterine muscle and cause dystocia in the presence of normal cephalo-pelvic relation. The position of the ring remains constant during labour and rupture of the uterus does not occur. The absence of rupture is explained by the fact that the upper segment is often relaxed and contracts ineffectively, whereas the lower segment is not excessively thinned out. The constriction ring is, therefore, associated with uterine inco-ordination.

### TYPES OF CONSTRICTION RING

(1) A spasmodic but reversible constriction ring which may relax under the influence of anæsthesia, incision, morphia and rest, adrenalin, magnesium sulphate and after death.

(2) A permanent non-reversible constriction ring which does not relax under anæsthesia, drugs or even after death as in the cases quoted by White, Phillips, Hannah, Massey, Carson and Michael. Those rings may be internal or external and may involve all three stages of labour.

The internal ring is commoner than the external ring in a proportion of more than 2 to 1 and the first stage is more liable to be affected than the second stage in the same proportion.

We are not concerned in this lecture with the third stage.

**FREQUENCY.**—This is bound to vary with the interest, or shall I say, the "ring consciousness" of the observer but the figure varies between 0.26 and 1.67 per cent. The second figure, I would say, is ridiculously high.

**LOCATION OF CONSTRICTION RINGS.**—A ring may occur at the external or internal os, at the junction of the upper and lower segments or at any level of the upper and lower segments. It is possible, though most rare, for more than one ring to be present.

Assuming that the physiological retraction ring is at the level of the upper border of the symphysis pubis at the onset of labour (Rudolph, Smyly, Lahs and Reynolds) and that during a normal second stage, the ring rises 6-8 cm. above the symphysis pubis, the fact that in a series of 272 cases described by Rudolph in 1935, the ring was found behind the symphysis at a distance of 7-8 cm. above the external os, is fairly conclusive that the ring in that situation was in the lower segment. When constriction rings appear above the symphysis pubis, either externally or internally, they may be due to a constriction of the physiological retraction ring or annular spasm at different levels of the upper segment. It can be said definitely, therefore, that a ring behind the symphysis pubis is a true constriction ring in the lower uterine pole, very probably at or near the internal os.

Rudolph, in 56 cases reported in 1947, found the ring :—

(a) In the region of the "obstetric" internal os—40 cases or 71 per cent.

(b) At the junction of the upper and lower segments—9 cases or 16 per cent.

(c) In the upper uterine segment—7 cases or 13 per cent.

## **PATHOLOGY**

When the ring is visible, a transverse sulcus may be observed running across or involving only one half of the abdomen at different levels above or below the umbilicus; it is usually stationary. The uterus above may manifest normal tone or a varying degree of tetany during labour; the uterus below may be ballooned out, may manifest normal tone or may be atonic. Examination of specimens shows that at the site of the permanent constriction ring, the transverse muscle fibres are responsible for the ring formation; the longitudinal muscle fibres are neither contracted nor retracted.

*Effect on Labour.*—Labour is prolonged. In the first stage the ring interferes with uterine polarity and arrests the retraction of the upper segment and formation of the lower segment. The ring makes it impossible for the presenting part to come into firm contact with



the lower uterine pole; the presenting part, therefore, lies loose in the cavity and there is no descent. In the second stage the efficiency of the uterine contractions is impaired and there is neither descent nor internal rotation. Uterine rupture may result only very rarely if an ischæmic necrosis is present. When the ring relaxes a normal mechanism should obtain.

## DIAGNOSIS

*Absolute.*—This is made by noting the presence of an external constriction ring or by intra-uterine palpation of the ring.

*Speculative.*—The patient is very often of the introspective type and a history of a close relative having suffered a long and protracted labour may be obtained. Pain is present in the back rather than in the abdomen, is constant and is aggravated during a contraction. Phillips stresses the importance of noting that the pain of a uterine contraction persists after the palpable hardening, brought about by uterine contraction, has passed off. In normal uterine action a sensation of pain is not experienced until the uterine contraction is well established and the pain should normally cease before the contraction is finished. This can be judged by the palpating hand. The sensation of pain usually occurs when the intra-uterine pressure reaches 25-30 mm. Hg. Where uterine muscle is in spasm, the interval pressure, as we shall see presently, approaches that level and so therefore pain is felt at the very beginning of a contraction. Ischæmia of spasmodically contracted muscle or increased uterine tension may play a large part in the production of such pain. The uterine contractions vary in frequency, intensity and duration. Sometimes, on the other hand, they are rhythmic and strong but their intensity does not appear to increase as labour advances. There may be the desire to "bear down" with the os still far from full dilatation and it is thought that this may be due to spasm in the colon or rectum. At intervals the contractions may be colicky and most severe.

The following are suggestive findings made on vaginal examination:—

(1) Looseness of the presenting part during a uterine contraction with failure to advance in the second stage.

(2) The head may actually rise during labour.

(3) Laxity of the cervix during the height of uterine contractions, the cervix lying loosely around and below the presenting part.

(4) Absence of impact of the presenting part on the examining finger during a uterine contraction.

Exhaustion need not be a feature if the labour is managed properly.

## PROGNOSIS

This depends on correct diagnosis and the institution of proper treatment (Rucker).

The main danger to the mother is trauma which may involve the

uterus, cervix, vagina and adjacent tissues from attempts to assist delivery. Others are intra-partum infection, exhaustion, shock and post-partum hæmorrhage associated with prolonged labour, continued uterine inefficiency and general anæsthesia.

Death or injury to the foetus may result from birth trauma or from intra-uterine asphyxia due to the interference with placental circulation by uterine spasm. (In normal labour the intra-uterine pressure in the intervals between contractions is 5-6 mm. Hg. during the first stage and 10-12 mm. Hg. during the second stage. When the uterine contractions are colicky, the resting pressure may be raised to 15-18 mm. Hg. or more and is often higher than the B.P. in the placental sinuses.) Intra-natal infection with organisms from the amniotic cavity may also cause neo-natal death or disease.

White.—Maternal mortality 31·5 per cent.; Foetal mortality 72 per cent.

Michael.—Maternal mortality 20-33 per cent.; Foetal mortality 40-86 per cent.

M'Gill (1941).—Maternal mortality 15 per cent.; Foetal mortality 46 per cent.

Herman Johnson (105 cases).—Maternal mortality Nil; Foetal mortality 5 per cent.

Rudolph (An analysis of 371 cases).—Maternal mortality 15 per cent.; Foetal mortality 46 per cent.

In Rudolph's own 21 cases the maternal mortality was 9·5 per cent, and the foetal mortality was 24 per cent.

## REMOTE PROGNOSIS

*Behaviour of the Uterus in Subsequent Labours.*—Inco-ordinate uterine action does not often recur in subsequent labours. Usually uterine efficiency improves with each pregnancy and this improvement would seem to depend largely on the degree of cervical dilatation reached in the previous labour. If half dilatation is reached, the probability is that inefficient uterine action will not recur.

## TREATMENT

Prophylactic measures include exercises in mental and physical relaxation during pregnancy. As soon as uterine action is seen to be abnormal and the contractions colicky, intensive medication with morphia, pethidine and other analgesics is essential.

It is of primary importance that each case must be judged on its own merits and it is impossible, therefore, to lay down a hard and fast scheme of treatment. At the same time, there is a general consensus of opinion against such heroics as Duhrssen's incisions with subsequent forceps delivery (the operator is not getting at the ring at all), manual dilatation, which, according to Polak, means "manual laceration," and version and extraction. All of those are associated with trauma, shock, sepsis and bad results to mother and child. A more

lenient view is taken by some—and it is only fair to say that this method finds more support in this country than elsewhere—of Willett's continuous weight traction. Rudolph, using this method, quotes a maternal mortality of 23 per cent. and a foetal mortality of 60 per cent. and maintains, I think rightly, that this treatment is only of value when the ring shows a tendency to relax under anæsthesia or drugs. It would seem to me that the greatest difficulty in assessing the correct method of treatment is when and how to interfere.

I would mention three different methods of treatment :—

(1) Ultra-conservative treatment.

(2) Anæsthesia or antispasmodic drug therapy with, if successful, delivery by forceps.

(3) Cæsarean section.

(1) *Ultra-Conservative Treatment* (Rudolph).—This may be expressed as “intelligent expectancy.” Labour is considered to be prolonged at 18 hours with the cervix showing little or no dilatation. This is the time to anticipate exhaustion and it is well to remember that in some patients there may be 8-10 hours of prodromata before the actual onset of pains when little food or drink may be taken—a factor which may predispose to exhaustion.

When the first stage has progressed for 18 hours an intra-uterine examination should, if possible, be made. If a constriction ring is present and there is neither maternal nor foetal distress, the patient may be left for another 8-10 hours. If, at the end of that time, there is still no indication for interference, the ultra-conservative method of treatment should be decided upon. The urine should at once be tested for acetone, etc., and this should be repeated at twelve-hourly intervals. The diet, liquid or soft, should consist of 3000 calories of food rich in carbohydrates and 2000 c.c. of water in each 24 hours of labour. Sedation (morphia or omnopon) should be such as to ensure adequate rest and sleep, pethidine, 100 mg., to relieve pain spasm. A negative acetone test should be the criterion of proper management. It is true that some give antispasmodics during the first stage of labour but that is not true conservative treatment.

With such careful supervision, and provided the membranes are intact, a patient may be carried through a first stage of 100 hours and may continue for 9-10 hours in the second stage waiting for spontaneous relaxation and descent of the head which make vaginal delivery possible.

I would submit in the strongest terms that such a prolongation of the first and second stages, as has been suggested by those advocating this method, is wholly unjustifiable to both mother and child. To my mind the phase of “masterly inactivity” may pass into one of “useless procrastination.” If antispasmodic therapy does not relax the ring in the first stage, and it probably will not, I would, as a rule, unhesitatingly perform Cæsarean section. If the patient is in the second stage,

antispasmodic drugs may be tried and an attempt at vaginal delivery made as soon as possible.

(2) *Anæsthesia, Antispasmodics and Forceps Delivery.*—In the first place, it should be noted that this method may eventually have to be employed where conservative treatment has failed—where the ring has refused to relax spontaneously.

Regarding anæsthesia, there is absolutely no agreement. Deep chloroform anæsthesia is favoured by some, æther by others. Ethylene, nitrous oxide and oxygen and spinal anæsthesia are ineffective. Of the drugs three deserve mention—amyl nitrite, adrenalin and intravenous magnesium sulphate have all been given with varying and often quite unreliable result. Trinitroglycerine and prostigmine proved, according to Jeffcoate, quite ineffective. With the idea of paralysing the sympathetic, he also tried tetra ethyl ammonium chloride, the initial intravenous dose being 0.25-0.3 grammes and this he repeated on several occasions, the largest amount given to one patient being 1.5 grammes in the course of 9 hours, again with little or no success.

Souter and Miles Phillips advocate amyl nitrite in a dosage of 5 m.

With adrenalin the routine is as follows:—Introduce the hand into the uterus in contact with the ring. Give subcutaneously 5-10 m. of 1 in 1000 adrenalin and wait for five minutes when the action should be apparent. If there is no relaxation another 5 m. should be given. Adrenalin causes contraction of uterine muscle and is thought to affect mainly the lower segment. It follows, therefore, that the upper segment may be, to some extent, inhibited. On this assumption it is difficult to see what action adrenalin can have in relaxing a lower segment ring.

Intravenous magnesium sulphate may be given in a dose of 2 c.c. of a 50 per cent. solution or 10 c.c. of a 20-25 per cent. solution. Magnesium gluconate, which has a more lasting action, may be given intravenously as 10 c.c. of a 20 per cent. solution.

Abarbanel advises this therapy for conditions other than constriction ring. For example, he gives magnesium sulphate before using oxytocics in the induction of labour, in an incarcerated but separated placenta in the third stage following an oxytocic given when the anterior shoulder was born, after pains which may be aggravated by ergot preparations and in spasmodic dysmenorrhœa where, he says, relief may be given for 8-10 hours by one injection.

Where anæsthesia or drugs fail to relieve the spasm, Cæsarean section should be performed or, in a few where maternal exhaustion is apparent or the fœtus dead, craniotomy and/or embryotomy may be necessary.

(3) *Cæsarean Section.*—I would say that this should be the method of treatment in the vast majority of cases. It should be done in the interests of the child and particularly if there are signs of fœtal distress. It should be done too for both mother and child when the labour is unduly prolonged and where more conservative treatment has failed. In the elderly primigravida it may not be justifiable to wait until fœtal

distress has developed ; in other cases section may be the better procedure for the mother even if the child be dead. Using the lower segment route and with appropriate chemo-therapy, section may be the safer method of delivery even in the prolonged labour associated with early rupture of the membranes or where a tentative attempt at forceps delivery has failed. I do not suggest that such a " combined operation " is an attractive proposition but I paint this rather gloomy picture deliberately to make the point that, where the circumstances are anything but ideal for abdominal operation, section may be less harmful than a difficult vaginal delivery associated with much trauma and shock. Some will say " section is the easy way out—the cowardly way." To them I would reply that it is preferable to be an " obstetric coward " in the presence of a mother happy with her child than an " heroic one-way-minded obstetrician " when that is the vaginal way leading to foetal and maybe maternal death.

Section is being done more frequently and the results depend, to a large extent, on the time of diagnosis and the number of vaginal operative procedures attempted before section is undertaken. This method of treatment, however, is not the complete answer to successful management. If done too early, an absolute diagnosis may not be possible and at the time of section no ring may be found ; if done too late, the conditions may not be so good for abdominal operation and the life of the child may be jeopardised.

You may remember I began this lecture by referring to a paper by Professor Robert Jardine on " The Retraction Ring as a cause of Obstruction in Labour." May I read you his suggested management of such a case. " If the child is alive I am convinced that Cæsarean section is the proper treatment. Full doses of morphia or opium have been recommended but I have never seen any effect in causing relaxation in a number of cases where morphia has been used freely. Manual dilatation has also been advised but the hand is powerless in such cases. Incision of the ring has been advised but it would be impossible to prevent the incisions extending and this would end in rupture of the uterus. Hydrostatic bags are useless as you cannot introduce them high enough to bear upon the ring. If the child is dead, it could be delivered by craniotomy, provided you have an instrument which will enable you to make powerful traction. If the shoulders are caught the clavicles should be cut." In the discussion which followed Berry Hart favoured nitrite of amyl if deep chloroform anæsthesia failed to relax the ring.

## II. UTERINE INERTIA

Blair Bell was of the opinion that inertia, primary and secondary, was a single clinical entity although it may make its appearance at different stages of labour. In recent years there has been increasing support for this view and it is preferable to refer to " secondary inertia " which may result from mechanical obstruction as " uterine exhaustion."

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Œstrogenic substance was variable in its oxytocic effect. No reaction occurred prior to the 29th week of pregnancy. After that time the number of patients who responded increased progressively as pregnancy advanced. The œstrogenic substance increased both uterine tonus and the various characteristics of the uterine contractions but the nature and degree of the responses were unpredictable.

The tocograph criteria of a normal labour are :—

- (1) Marked resemblance in the pattern of successive waves.
- (2) The contractions should be of average strength.

According to Lorand, primary inertia is characterised by :—

- (1) Weak contractions.
- (2) Arrhythmia.
- (3) A failure of the contractions to resemble each other.

Recordings may, therefore, detect early in labour, poor uterine motility and prompt treatment for inertia may be instituted.

Lorand, using his tocograph, recognises three forms of primary inertia :—

- (1) The hypotonic.
- (2) The normotonic.
- (3) The hypertonic.

This classification is most important from the point of view of treatment. Hypotonic inertia is characterised by a loss of tone in both upper and lower segments. It is, therefore, a true inertia with feeble activity of the uterus as a whole. There may be slight abdominal pain during a uterine contraction but otherwise there is little or no discomfort and it is often difficult to say whether or not the patient is in labour. With the normotonic and hypertonic varieties, the picture is different. In the hypertonic form, the commonest inertia, there is usually an increased tone and resistance to dilatation of the lower pole associated with a weak action of the upper segment. This is referred to as reversed polarity. On occasion, however, a rise of tone may be provided by intermittent, infrequent and irregular spasmodic contraction of the upper segment. There is persistent backache and the abdominal pain, as in constriction ring dystocia, is apparent before and after the palpable hardening of the uterus. It may indeed persist between contractions. The desire to "bear down" in the first stage, a feature which is quite often most disconcerting, is thought to be due to spasm of the pelvic colon or rectum.

## TREATMENT

The broad principles of any prolonged labour apply. Whatever the type of inertia, sedation—and morphia is best—is indicated at night. Fluids and carbohydrates are essential. Some advise 2 oz. of castor

oil, an enema and a hot bath on the second day. Prophylactic sulphonamide and penicillin may be indicated on the third day, or before that time if the membranes rupture early. When labour advances to a certain stage—half-dilation of the cervix—malposition may be corrected with good effect. There is a small place for cervical incisions or manual dilatation when the head is low in the pelvis.

Two forms of treatment deserve special mention :—

- (1) The use of oestrogens and oxytocics.
- (2) Cæsarean section.

(1) *Oestrogens*. Murphy has demonstrated that a certain number of patients experience a moderate increase in tone during labour. On that basis the exhibition of an oestrogenic substance might raise the tone and be of value in primary inertia. He found an increase of tone resulting from oestrogenic therapy in 25 per cent. of normal patients. Against that idea there are the views expressed recently at a meeting of the North of England Obstetrical and Gynæcological Society. Snaith and Jeffcoate, giving oestradiol in propylene glycol intravenously in doses which varied from 125 mg. total dose to 500 mg. given in a single dose, reported that the results could not be regarded as significant and that this form of therapy was of doubtful value. Jeffcoate further reported that if such an injection was given when the abdomen was opened there was no immediate effect on uterine contractions or vascularity.

*Oxytocic Drugs*.—Rational therapy can be carried out only after uterine wall tone has been ascertained by the tocograph or some similar instrument. An oxytocic drug administered to a patient exhibiting a high uterine wall tension has little effective value in inducing or augmenting clonic activity. Under such conditions the uterine wall is already so much contracted that there exists little opportunity for further contraction—at least of a clonic variety. And so, if a patient with a high uterine tone receives an oxytocic drug, the result is further tightening of the uterus and may be tetanic spasm. The effectiveness of an oxytocic drug is, therefore, in inverse ratio to the degree of uterine tone. Where the tone is high morphia is the drug of choice, with pethidine during the day, and good results sometimes obtain from rupture of the membranes. Where the tone is low pituitary extract is indicated. Reid and Eastman advise small doses of pituitary extract and Reid begins with 1 m. and increases by 1 m. at 30-40 minute intervals, if necessary, up to a single dose of 4 m. Eastman, on the other hand, begins with  $\frac{1}{2}$  m. and never gives more than 1 m. which may be repeated half-hourly up to a total dosage of 4 mm. He claimed that this reduced mid-forceps application, cervical incisions and even section. There are certainly cases where the oxytocic drug may result in foetal death but if given to the proper case this possibility is unlikely and makes for a lower foetal mortality than might otherwise result from manipulative delivery.



The accidents which have followed the use of oxytocic drugs in inert labours have resulted from :—

- (1) A poor selection of patient.
- (2) Excessive dosage.
- (3) Misuse of the drug in cephalo-pelvic disproportion and high uterine tone.

(2) *Cæsarean Section*.—The place of this operation is again a most important one. Each case, however, must be considered individually. Where the patient is an elderly primigravida, where the membranes have been ruptured for 24 hours or more, where there are signs of maternal or foetal distress and where more conservative treatment has failed, there is a very definite place for section.

If operative interference is necessary, spinal or local anæsthesia may be preferable to inhalation anæsthesia if post-partum hæmorrhage is to be avoided.

And so I think it is fair to say that in the last 36 years the terminology, as it applies to the conditions under review, may have altered slightly but the ætiology is still uncertain and the treatment remains much the same. Should the obstetrician ever be inclined to complacency it is well that he should ponder those facts for they are humbling.

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## REGIONAL ILEITIS

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### INTRODUCTION

IT is always refreshing and exciting in medicine when someone discovers a new disease, and it is always a challenge to the rest of us to say if it has not been occurring hitherto. The past twenty years have not been particularly fruitful with new diseases, but one can consider the claims of "eosinophilic granuloma of bone"—that benign inflammatory lesion of bone described as a clinico-pathological entity by Jaffe in 1940; "Bornholm's disease"—that condition of painful tender muscles with temperature which is thought to be an epidemic myalgia; "Reiter's disease"—the triad-syndrome of non-specific urethritis, arthritis and conjunctivitis; and the "crush syndrome," in which Bywaters drew attention to the renal damage following the crushing of limbs by fallen masonry early in the war. You may think of others, and you may cast legitimate doubts as to their newness; and yet we must give credit to these workers who, if they have done nothing else, have tried to isolate and classify a group of clinical and pathological features from the midst of obscurity.

Crohn<sup>1</sup> and his co-workers described in 1932 what they claimed was a new entity—"a disease of the terminal ileum, affecting mainly young adults, characterised by a subacute or chronic necrotising and cicatrising inflammation." Their original definition of the disease was based on a study of fourteen cases, and the features that they described of mucosal ulceration leading to stenosis of the lumen of the intestine, the tendency to fistula formation, the clinical features of colicky abdominal pain, diarrhoea, and loss of weight, have become recognised throughout the world as the salient points of this apparently new disease. The conception of how much bowel can be involved has been broadened, and it is believed that isolated areas of jejunitis, "skip" areas in the ileum, and affection of the colon in association with the ileitis are all part of the same process. Classically, and in the great majority of cases, however, it is the terminal ileum alone that is affected; and the cause of the condition remains a complete mystery.

### CLINICAL FEATURES

Regional ileitis appears to have four characteristic phases, and the clinical features of each are now well recognised:—

(1) It may be seen as an acute illness, indistinguishable pre-operatively from acute appendicitis. At operation the terminal segment

A Honyman Gillespie lecture delivered on 20th October 1949, based in part on a Thesis submitted to the University of Edinburgh for the Degree of M.D.

of ileum is found to be reddish-purple in colour, sodden and œdematous to feel, and obviously acutely inflamed.

(2) In the chronic phase the bowel wall is grey and rigid and the mucosa ulcerated; and the symptoms are characteristic—colicky abdominal pain, diarrhœa, loss of weight and a mild secondary anæmia. The symptoms are those of other forms of severe enteritis, except that in regional ileitis the diarrhœa is usually non-bloody.

(3) Symptoms of subacute intestinal obstruction may develop when the ileum becomes stenosed in the final stages.

(4) Fistulas may be a feature, either as an external fæcal fistula, or as an internal fistula to some adjacent viscus such as bladder or female pelvic organs, and causing bizarre symptoms.

### PATHOLOGICAL FEATURES

*Acute Ileitis.*—The length of bowel involved varies from 3 to 18 inches. Typically the swelling and redness are most marked at the ileo-cæcal valve and immediately proximal to it, the process fading off as the bowel is traced proximally. Sometimes the transition from inflamed to normal ileum is a gradual one, but in most cases there is quite a sudden clear-cut line of demarcation.

In the acute stage the cæcum is not involved, and it is very striking how this obviously acute process stops short at the ileo-cæcal valve as if a barrier had been raised. The mesentery of the affected portion of ileum is greatly thickened and œdematous and contains enlarged glands. These glands are soft, and sometimes they may be broken down to abscess formation.

The microscopic appearance of the bowel wall in this phase is rather hypothetical; our knowledge is scanty because few specimens are resected at this stage. Crohn describes ulcers in the mucous membrane—scattered small discrete ulcers on the mesenteric border. Dixon<sup>2</sup> mentions solitary ulcers and enlarged mesenteric glands. Erb and Farmer<sup>3</sup> reported two cases showing widespread mucosal ulceration and marked œdema of the submucosa. The evidence of such reports is not very convincing because of doubt whether these few cases really were examples of regional ileitis; and, if so, whether they had not passed beyond the acute phase.

*Chronic Ileitis.*—This is the stage at which mucosal ulceration predominates and there are symptoms of intestinal irritation. Varying stages of acute, subacute and chronic inflammation may be seen, with variation in preponderance of polymorphs, lymphocytes, plasma cells and fibroblastic elements. This process is usually limited to the distal 10-14 inches of the terminal ileum, including the ileo-cæcal valve and terminating abruptly at that point. The most advanced changes are present at the valve, which in some instances is converted into a rigid diaphragm with a small irregular opening. Proximally the process gradually abates, but the shading off to normal mucosa

may be rather an abrupt one. The normal intestinal folds are distorted and broken up by the destructive ulcerative process, and rounded and blunted by œdema, giving a cobblestone appearance to the surface of the mucosa.

The mucosal ulceration is principally confined to the mesenteric side of the bowel, and the ulcers themselves are circular, oval or linear in shape, with deep crypt-like appearance and pouting mouths. Crohn remarks that the linear ulcers may either be original ulcerative lesions, or mechanical erosions due to the formation of a "darmstrasse" by the shortening of the fibrotic mesentery; it is difficult to say which. There is usually a marked capillary dilatation throughout the mucosa, but only slight fibrosis, and there is a dense infiltration of plasma cells and polymorphonuclear leucocytes.

The submucous, and to a less extent, the muscular layers are the seat of marked inflammatory hyperplastic and exudative changes. The inflammatory infiltration is somewhat different from that of the mucous membrane, being mainly of lymphocytes and plasma cells and sometimes eosinophil cells. The capillaries are widely dilated, and there are many fibroblasts and some collagenous fibrosis.

The subserous coat shows congestion and patchy infiltration of small lymphocytes. The serous coat is congested, but there are no polymorphs or exudation to be seen, *i.e.* no evidence of peritonitis. In the very late stages focal areas of reaction are seen in the serosa, giving the appearance on gross examination of tubercles.

As a result of the infiltration and fibrosis the wall of the bowel becomes enormously thickened and the lumen is encroached on. The mesentery becomes chronically thickened and shortened and fibrotic, and it contains enlarged soft nodes in which may be seen many of the histological features noted in the bowel wall. Abscesses in the mesentery are quite common and lead to adhesions and fistula formation.

Two other features are sometimes seen in the submucosa: (*a*) small abscesses, with walls densely infiltrated with polymorphs, some of which abscesses are cross-sections of deep sinuses leading to a mucosal ulcer; (*b*) occasional small tubercles, consisting of endothelial cells and giant cells. The giant cells vary considerably in size, with nuclei varying in number from one to very many and arranged irregularly or peripherally. Caseation is never seen in any of these tubercles.

Hadfield<sup>4</sup> made an interesting study of the pathological changes in twenty cases of regional ileitis, and claimed to have shown that the primary histological lesion was in the submucosa. Mucosal ulceration, which was always present, was thought to be secondary to the submucosal thickening. In some the ulceration was deep, with sinuses and ulceration in the various layers of the intestinal wall; but where the ulceration was slight, with little penetration of the submucosa by diffuse inflammatory cellular exudate spreading from the ulcer floor, then two striking changes were seen in the submucosa: (1) widespread

hyperplasia of its lymphoid tissue ; and (2) obstructive lymphœdema. Characteristically a germinal centre would be replaced by proliferating endothelial cells, which were sometimes aggregated to form a Langhan's giant cell. Non-caseating giant cell systems, not containing acid-fast bacilli, were seen in 13 of Hadfield's 20 cases.

Many writers have commented on giant cells in the submucous and muscular layers, and it is the presence of tubercles and giant cells that has added weight to the suggestion that this granulomatous condition is an unusual form of tuberculosis. In Crohn's view these giant cells are not an essential feature of the pathological pictures, but accidental findings due to the inclusion of small particles of vegetable matter which have become entrapped in the ulcers, entered the lymphatics and become encapsulated in the process of healing. The giant cells are regarded as part of the foreign body reaction. Hadfield, on the other hand, believes that the earliest, and possibly the specific histological lesion of regional ileitis is lymphadenoid hyperplasia, with the formation of non-caseating giant cell systems in the submucosa.

### TREATMENT

There is universal agreement that some form of surgical treatment is necessary in chronic regional ileitis, but that when the disease is encountered in the acute phase at operation nothing should be done. There is at least a 50 per cent. chance that the acute ileitis will resolve spontaneously ; the others will go on to the chronic stage and require surgery. It is usually safe to remove the appendix if readily accessible ; but it should not be removed, for fear of a fæcal fistula, in the presence of a mesenteric abscess associated with the ileitis. Medical treatment may be necessary in some chronic cases when preparing them for operation or when operation is refused or not feasible, and it consists of a generous high calorie, high protein, high vitamin, low residue diet, combined with a course of succinyl-sulphathiazole, and repeated small blood transfusions if necessary.

There are two schools of thought as to what is the best form of operative treatment for chronic regional ileitis—"radical resection," and "short-circuiting with exclusion." Garlock and Crohn<sup>5</sup> at the Mount Sinai Hospital have had longer and more extensive experience of treating regional ileitis than others, and while they used to practice a radical resection (right hemicolectomy), they now believe that a more conservative procedure carries a lower operative mortality and lower incidence of recurrence. They advise transection of the ileum proximal to the affected portion, and side-to-side anastomosis between proximal ileum and transverse colon. A simple short-circuiting operation without transecting the ileum is ineffective ; but when the distal ileum is divided, and thereby excluded from passage of intestinal contents, the ileitis proceeds to natural healing. Crohn and Garlock state that in the course of 25 instances in which a two-stage resection was undertaken the specimen, when finally removed after a variable

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interval, showed in almost every case advanced healing and scar replacement; and meantime internal and external fistulas also closed spontaneously. In favour of these views they quote their own figures:—

	<i>Number</i>	<i>Deaths</i>	<i>Recurrences</i>
Ileocolostomy with exclusion . . . . .	57	0 (0 per cent.)	6 (10.5 per cent.)
One stage resection . . . . .	45	6 (13.3 per cent.)	6 (15.4 " )
Two stage resection . . . . .	16	2 (12.5 " )	4 (28.6 " )

On the other hand, Dixon<sup>6</sup> still holds to radical surgery, with resection of the diseased segment of bowel along with the right half of the colon. He states that at the Mayo Clinic they performed resection (most often a one-stage procedure) in 108 cases of regional ileitis with only two deaths. In Dixon's experience the exclusion type of ileocolostomy did not bring about complete recovery, nor did fistulas close until the diseased segment was finally removed.

It is difficult to reconcile these divergent views, and we shall have to await further experience before being definite on the point. Certainly the less radical short-circuiting operation must be a less dangerous procedure in these cases where adhesions and fistulas are abundant; and it should seldom now be necessary to resect the specimen in order to establish the diagnosis. My feeling is that I would prefer to resect the specimen if the hemi-colectomy looked like being technically easy; and to content myself with short-circuiting and exclusion in difficult circumstances.

The question of why recurrences occur proximal to the line of anastomosis has never been satisfactorily explained. Three theories have been put forward: that the surgeon has failed to recognise a small "skip" area higher up the intestine; that a focus of infection has remained in a mesenteric lymph node not excised at operation; or that the unknown cause of the disease has continued to operate and produced a further out-crop of ileitis. There are no instances of unexplained recurrences among the eight cases of regional ileitis described below; and the only "skip" area that I have seen was in an adjacent loop of ileum that was adherent to the main mass (Fig. 16).

#### CASES PERSONALLY OBSERVED

The following abridged case notes are of eight patients with regional ileitis I investigated personally. The youngest was 18 and the oldest 49. I have seen at operation seven other cases, but they occurred during Army service abroad or in other circumstances making full investigation difficult.

The eight cases in this series had many points in common: they were all in good health until the onset of symptoms; they revealed no evidence of tuberculosis in lung or elsewhere either at the time of operation or during the years they were subsequently observed; there was never any history of dysentery, and no organisms of the



typhoid-dysentery group were found in the fæces ; the Wassermann reaction in all cases was negative. Cases 1 and 2 are examples of acute regional ileitis, which apparently resolved spontaneously. The other six cases were more chronic and required surgical intervention. These latter patients were all frightened to eat because it brought on abdominal pain, they had lost weight, and they showed a moderate degree of secondary anæmia.

I. J. W. (18). Female. Nurse.

*History*.—Acute abdominal pain for 36 hours. Constantly present in right lower abdomen with occasional stabs of colic. Accompanied by vomiting, but no diarrhoea. Similar attack lasting 48 hours three months previously, but otherwise has always been well. Admitted as an emergency ; thought to have acute appendicitis.

*On examination*.—Healthy looking young woman. Temp. 99° F. Tender and rigid over McBurney's point. No palpable mass.

*Operation* (1.6.37).—The terminal 10 inches of ileum was inflamed and œdematous, dark red in colour but with a visceral sheen (Fig. 1). The wall felt thickened and sodden, like wet blotting paper. The lumen felt patent but slightly narrowed. The mesentery was œdematous and the lymph nodes soft and enlarged. Cæcum, appendix and pelvic organs were normal. The appendix was removed (and histologically shown to be normal), and the abdomen closed without interfering with the acute regional ileitis.

*After History*.—Patient made a full recovery. When examined two years later she was free of symptoms, nothing abnormal was palpable in the abdomen, and X-ray barium series was negative. By correspondence in 1949 she informed me that she has remained well.

II. W. S. (30). Male. Ticket-collector.

*History*.—Sharp colicky abdominal pain for 12 hours, the pain gradually localising in the right lower abdomen. No nausea or diarrhoea. Similar attack nine weeks previously lasting 24 hours. Previously quite healthy. Admitted as an emergency, with the diagnosis of acute appendicitis.

*On Examination*.—Fit looking young man, not distressed. Temp. 97·8° F. Moderate tenderness in right iliac fossa but no rigidity. No palpable mass.

*Operation* (6.6.38).—The terminal 12 inches of ileum were acutely inflamed, reddish-purple in appearance and "soggy" to feel. Clear demarcation line proximally and at ileo-cæcal junction. Mesentery œdematous, with numerous soft glands. Appendix normal. The condition was regarded as acute regional ileitis. The appendix was removed, and the abdomen closed.

*After History*.—Patient made a good recovery. One year later he stated that he had had three similar attacks of abdominal pain lasting 24 hours, but no other complaints. Bowels moving once a day. An X-ray barium series at this time showed no signs of stenosis in the terminal ileum (Fig. 14). In 1942 patient was killed in action.

III. H. W. (40). Male. Civil Servant.

*History*. Colicky abdominal pains for a year, getting progressively worse. Tendency to diarrhoea originally, but now rather constipated and distended. Some slime but never any blood in motions. Considerable loss of weight.

*On Examination*.—Wasted ill-looking man. No fever. Abdomen reveals subacute intestinal obstruction, with visible peristalsis. Sausage-like tumour

palpable in right iliac fossa. A straight X-ray film of the abdomen showed fluid levels in small intestine.

*Operation* (3.12.36).—Gross contraction of terminal 5 inches of ileum, the bowel wall feeling more like a firm solid stalk than a healthy yielding tube. Sudden change proximally to normal, though distended, ileum. Mesentery thickened and œdematous, with enlarged glands. Cæcum not involved. A right hemi-colectomy was performed, with side-to-side anastomosis between proximal ileum and transverse colon.

*After History*.—Patient died three days later. Post-mortem examination showed a leaking anastomosis. The stitches had cut out of the friable distended ileum.

*Pathological Examination*.—Macroscopic as seen in Fig. 4. Microscopic (Fig. 13). There is no widespread ulceration, but in places the *mucosa* is breached by narrow sinus-like ulcers passing deeply into the muscle coat. The *sub-mucosa* shows œdema, diffuse polymorph and plasma cell infiltration, collagenous fibrosis. Many distended lymph channels and increased number of lymphoid follicles. No tubercles. The other layers of the bowel wall show minor degree of chronic inflammation. *Lymph node* shows enormous dilatation of lymph sinuses. Cæcum was unaffected.

Section from ileum stained Ziehl-Neelsen revealed no tubercle bacilli. Guinea pigs inoculated with tissue from the wall of ileum showed no evidence of tuberculosis when killed after six weeks.

IV. E. M. (22). Female. Housewife.

*History*.—Lower abdominal pain, worse on right and griping in character, for ten months. Increasing looseness of motions, the bowels now moving 4-5 times a day. Never noticed any blood in stool, but occasionally some slime. Lost one stone in weight. Feels tired, has a constant slight headache and a general sense of malaise.

*On Examination*.—Pale thin woman. Fullness in lower abdomen, and palpable tender mass in right iliac fossa.

X-ray barium series: The terminal ileum is irregularly stenosed for 8 inches proximal to the ileo-cæcal valve—Kantor's "string sign."

*Operation* (21.6.38).—Terminal loops of ileum and cæcum matted together. On separating adhesions, the ileum alone was found to be involved, in its terminal 10 inches. It was reddish grey in colour and its wall felt firm and thickened. Mesentery was short and thick, containing large soft glands. A right hemi-colectomy was performed, with side-to-side anastomosis between remaining ileum and transverse colon.

*After History*.—Patient made a good recovery. Six months later she complained of a good deal of diarrhœa, but X-ray barium enema revealed no recrudescence, and symptoms were alleviated with low residue, high vitamin diet. In 1949, nine years after the resection, the patient is remaining well and putting on weight.

*Pathological Examination*.—Macroscopic appearance as in Fig. 5. Microscopically the *mucous membrane* shows deep ulceration on its mesenteric border, and dense infiltration of plasma cells and polymorphs. The *submucosa* (Figs 2 and 12) shows diffuse chronic inflammation, foci of reactive lymphoid tissue, abscesses, and occasional small "tubercles" with giant cells. The giant cells vary considerably in size and appearance: in some the nuclei are arranged peripherally, in others more irregularly throughout the cells; some contain a central mass of hyaline material, which is not doubly refractile by polarised

light. The *muscle* layer shows similar but much slighter inflammation and occasional small "tubercles." Fibrosis is limited to regions deep to mucosal ulceration. Cæcum and appendix were normal.

No tubercle bacilli seen; and guinea-pig inoculation proved negative.

V. J. A. (18). Female. Housemaid.

*History*.—Patient quite well until one week before admission, when she began to feel feverish and out of sorts, and to have constant dull pain in lower abdomen. The pain increased and she was admitted to hospital as an emergency. For past year had had occasional spasm of "windy" pains in the stomach. Bowels had been moving twice a day for the past three years. Never noticed any blood or slime in the motion. She had not been losing any weight, nor had she been gaining any.

*On Examination*.—A thin little girl, flushed and toxic. Temp. 100.2° F. Palpable tender mass in right iliac fossa, thought to be an appendix abscess.

FIG. 4.—Chronic ileitis. Stenosis of terminal ileum, causing intestinal obstruction. Cæcum and appendix unaffected.

FIG. 5.—Stenosis of terminal ileum. Mucosal ulceration on the mesenteric border.

FIG. 6.—Terminal ileum and cæcum immediately after resection. The fistula runs behind cæcum.

FIG. 7.—Tubercle in muscle. Endothelioid cells with a few polymorphs in centre. No giant cells and no caseation.

FIG. 8.—Interior of specimen in Fig. 6. Stenosis and ulceration of ileum. Probe in fistula. Well marked cæco-colic valve, but cæcum unaffected by disease.

FIG. 9.—Thickening and ulceration of terminal ileum. Cæcum and ascending colon unaffected. "Skip" area in ileum proximally.

FIG. 10.—Cross section of ileum and mesentery. Ulceration of mucosa and fibrosis in submucosa.

*Operation* (28.2.38).—Normal appendix. An abscess in the upper ileo-cæcal angle contained thick greenish-yellow pus. The terminal 15 inches of the ileum were greatly thickened and rigid, with a plum-colour congestion of the bowel and irregular whitish patches on the surface. The thickening stopped abruptly 15 inches proximal to the ileo-cæcal valve, and the ileum above was normal. Cæcum appeared normal except for redness and thickening where it was adjacent to the gland abscess.

A drain was inserted down to the abscess. The appendix was not removed.

*After History*.—Patient made a slow convalescence. She developed a fæcal fistula soon after the operation and was rather critically ill for several weeks. During the next nine months operations were performed to improve drainage of the abdominal abscess, for ischio-rectal abscess, and eventually a short circuiting ileo-transverse colostomy (without transection of ileum). Nevertheless one year after her first operation the patient still had a fæcal fistula, frequent bowel movements, and was becoming emaciated, so that on 23.2.39 the abdomen was opened again and a radical resection carried out of the involved ileum and right colon. There were many adhesions between bowel loops and to right ovary and tube, and several small abscesses in the anterior and posterior abdominal walls. The patient made a good recovery from the formidable procedure. She was well and her wound quite dry when seen six months later, but it has not been possible to trace her subsequently. It is believed that she went abroad early in the war.

*Pathological Examination*.—Macroscopic as in Figs. 6 and 8. Microscopic:

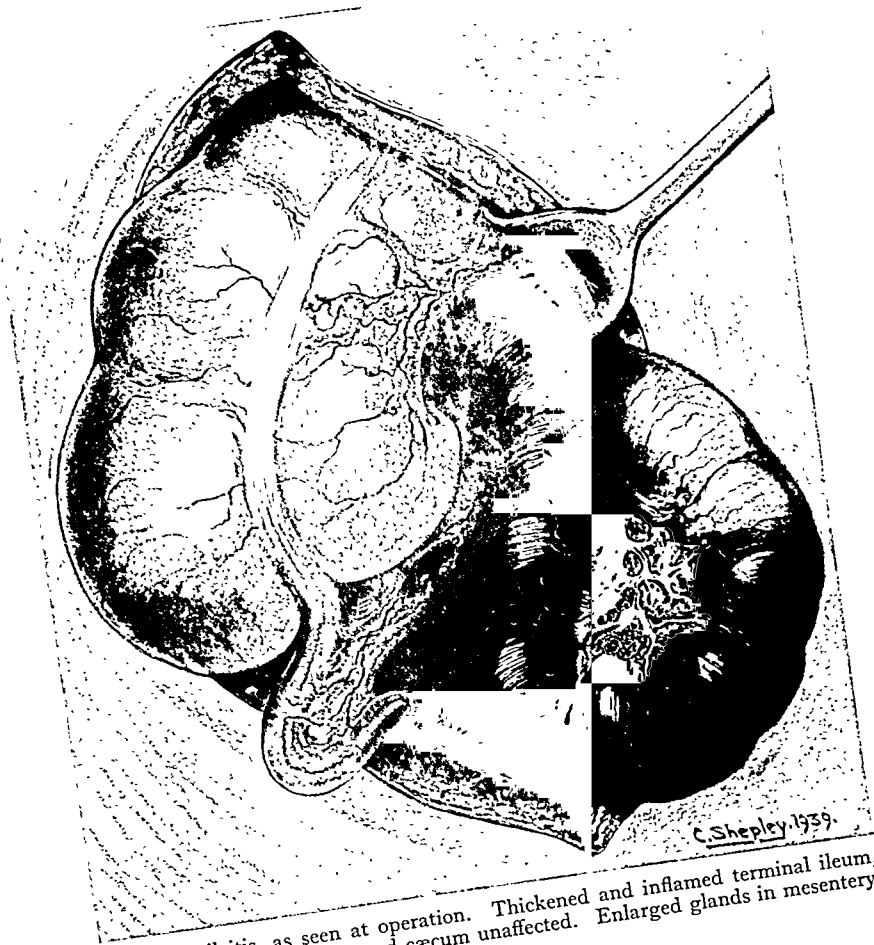


FIG. 1.—Acute ileitis, as seen at operation. Thickened and inflamed terminal ileum, with normal bowel proximally and caecum unaffected. Enlarged glands in mesentery.

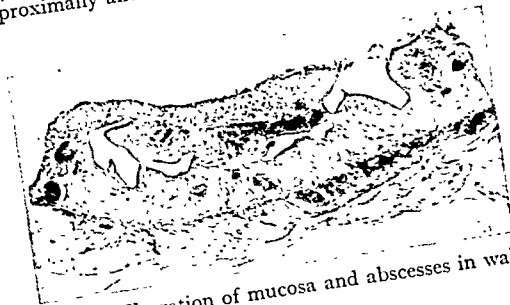


FIG. 2.—Ulceration of mucosa and abscesses in wall.

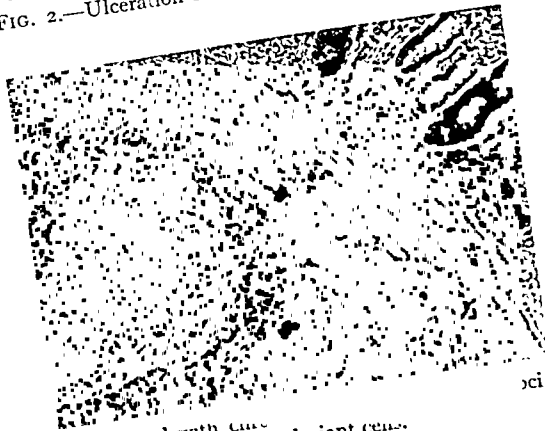


FIG. 3.—Submucosa infiltrated with cells and scattered giant cells.

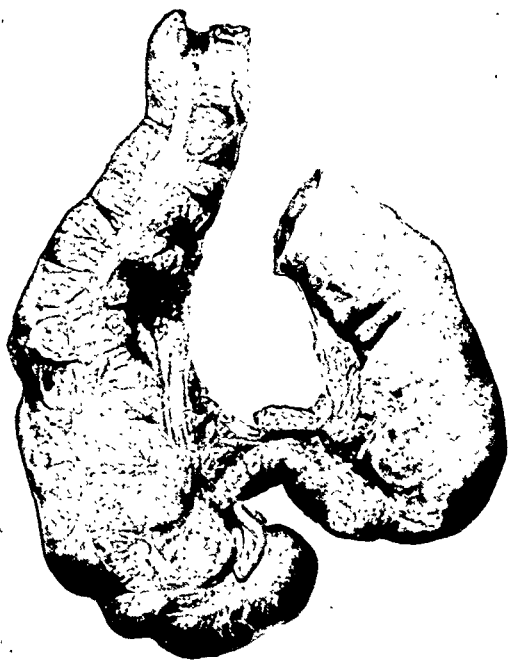


FIG. 4.



FIG. 5.

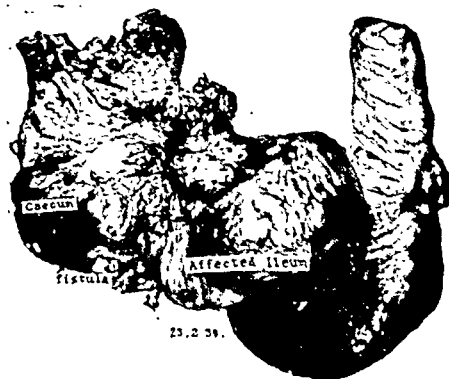


FIG. 6.



FIG. 7.

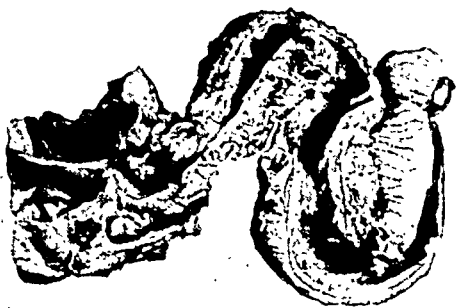


FIG. 8.



FIG. 9.

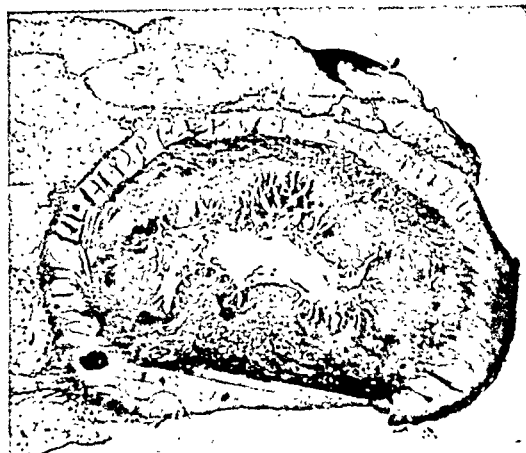


FIG. 10.

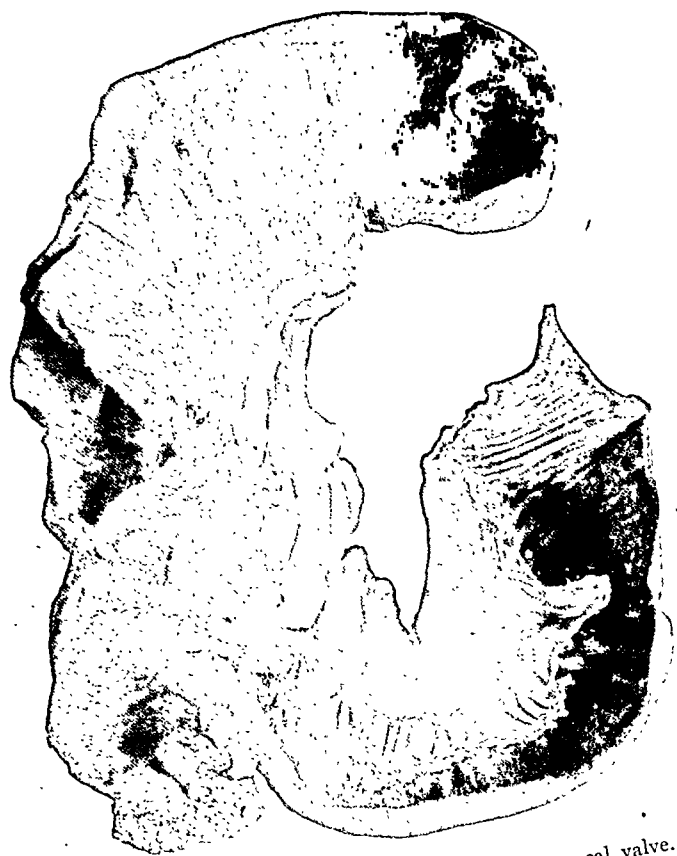


FIG. 11.—Thickening of wall of ileum, most marked at ileo-cæcal valve. Extension into cæcum as a firm ring at cæco-colic valve.

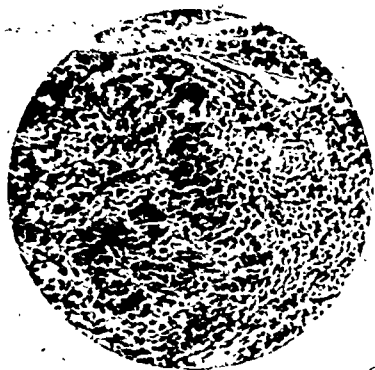


FIG. 12.—Tubercle in submucosa. Giant cells with peripheral nuclei. Hyaline in their interior.

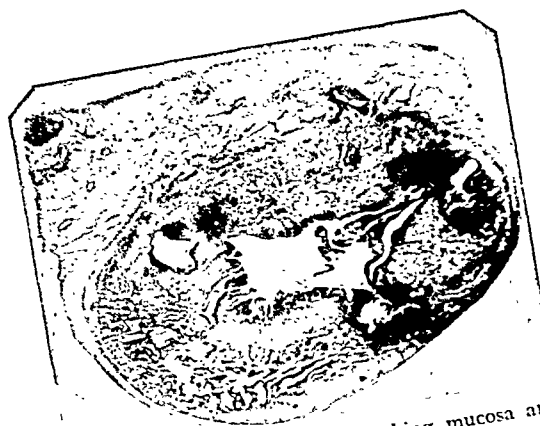


FIG. 13.—Sinus-like ulcers breaching mucosa and passing deeply into muscle. Œdema and fibrosis of submucosa.



FIG. 14.—X-ray, barium series. No stenosis or affection of terminal ileum seen eight months after attack of acute ileitis.

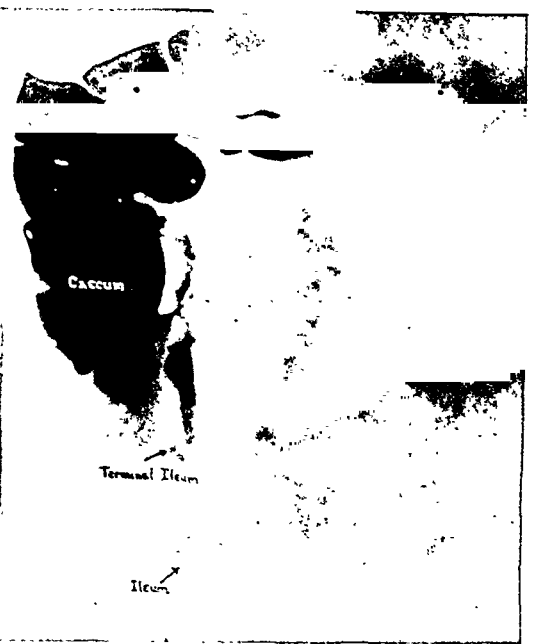


FIG. 15.—X-ray, barium series, Jan. 1939. Stenosis of terminal ileum (Kantor's "string sign").



FIG. 16.—Same case as Fig. 15, March 1939. Increase in extent of ileum involved compared with two months previously.



FIG. 17.—X-ray, barium series. Stenosis of terminal ileum with dilatation proximally. Caecum indurated.

the *mucosa* is ulcerated on the mesenteric border. The *submucosa* shows a moderate degree of œdema and fibrosis and a sparse plasma cell infiltration (Fig. 10). The *muscle* coat is hypertrophied, and one tubercle is seen. This is a very proliferative tubercle with many endothelioid cells and in its centre a few polymorphs, but no giant cells (Fig. 7). Cæcum and appendix were normal. An adjacent gland showed histiocytic reaction and one or two ill-defined tubercles.

No tubercle bacilli were seen on special staining; and guinea pig inoculation proved negative.

VI. I. C. (49). Female. Housewife.

*History*.—Admitted as an emergency, with severe colicky abdominal pain, vomiting, and diarrhœa for 24 hours. Two similar previous attacks in the past 7 weeks, lasting a few days. Previously healthy and no loss of weight, but the bowel movements have been more frequent (thrice daily) for three years. Never noticed any blood or mucus in motion.

*On Examination*.—Stout florid woman. Temp. 99.4° F. Tender and rigid in right iliac fossa. No mass palpable.

*Operation* (11.1.39).—The terminal nine inches of ileum were reddish-blue in colour, but the peritoneal coat was glistening. The ileum was slightly thicker than normal and on palpation the wall had the feel of raw meat. Proximal ileum, cæcum and appendix were normal. The mesentery was about half-an-inch thick with fat and œdema, and there were several enlarged soft glands. The appendix was removed, a gland excised for biopsy, and the abdomen closed.

*After History*.—It was thought that as this appeared to be a fairly acute case of regional ileitis there was a chance of the condition resolving spontaneously, which explains why nothing further was done at the first operation. The gland excised showed sinus distension and follicular atrophy, and yielded a growth of *B. coli* on culture. X-ray barium series (Fig. 15) was typical of regional ileitis. Two months later the patient was feeling well and her only complaint was frequency of bowel movement. A mass was now palpable in the right side, and X-ray barium series (Fig. 16) showed a marked and irregular stenosis of terminal ileum of increased extent compared with previous X-ray. Operation was advised but patient demurred because she felt well. Two years later she returned, having had many attacks of colicky abdominal pain and diarrhœa, but no loss of weight and no blood in the motion. Further operation was performed (29.9.41), when a mass of inflamed ileum and many adhesions were found. Resection was deemed inadvisable, and ileo-transverse colostomy performed with transection of ileum. When seen in 1949 the patient was keeping well, with occasional diarrhœa but no pain or loss of weight. A mass was still palpable in the right iliac fossa.

VII. E. B. (39). Female. Housewife.

*History*.—Four months' history of colicky abdominal pain, occurring two or three times a day and culminating in severe vomiting, so that she was admitted as an emergency, thought to have intestinal obstruction. Has had four bouts of diarrhœa lasting a few days, but never noticed any blood or slime in motions. Has been losing weight and becoming pale and easily tired.

*On Examination*.—Pale thin woman. Temp. 97.8° F. No visible peristalsis. Tender and rigid in lower abdomen. Suggestion of a mass in right iliac fossa.



*Operation (6.3.37).*—Terminal eight inches of ileum markedly affected and greyish in colour, slightly narrowed, and with a few small tubercles on the surface. On palpation the walls felt firm and thick, giving the feeling of a pliant fleshy cord. Mesentery thickened, but no visibly enlarged glands. The cæcum felt firm and irregular on its medial aspect. Appendix was normal, and it was removed. There was no evidence of intestinal obstruction, and it was decided to defer question of resection until patient was better prepared.

*After History.*—Patient continued to have colicky pains. X-ray barium series (Fig. 17) showed narrowing of terminal ileum and distortion of cæcum. Further operation was performed on 18.3.37 and the affected ileum, cæcum and ascending colon resected, with side-to-side anastomosis of proximal ileum and transverse colon. Thereafter progress was steady. A year later she had put on three stones in weight. When seen in 1949 she was again having occasional bouts of pain and diarrhoea. X-rays did not reveal any signs of recurrence, and patient was reassured; but recurrence may yet show itself.

*Pathological Examination.*—Macroscopic appearance as in Fig. 11. Greatest thickening is at ileo-cæcal valve extending into cæcum. Proximally it fades away gradually in ileum. Microscopic: *ileum*: the *mucosa* shows a few irregularly placed ulcers, and chronic inflammation. The *submucosa* shows marked fibrosis and an increase in number of lymphoid follicles. There are some abscesses connected to the lumen by sinuous tracks. *Muscle* shows collagenous fibrosis. The *serosa* and subserosa showed non-specific chronic inflammation, but no tubercles were seen throughout the section. *Cæcum*: the appearances in cæcum were exactly comparable to ileum.

No tubercle bacilli were seen on special staining, and guinea-pig inoculation proved negative.

#### VIII. M. A. (20). Female. Clerkess.

*History.*—Six years' history of colicky abdominal pain and constipation. During this period has had four bouts of severe illness, being confined to bed for a fortnight at a time with fever, pain, vomiting and diarrhoea—bowels moving 8-10 times a day, occasionally accompanied by light blood. Has lost 7 lb. in weight in past year.

*On Examination.*—Pale thin girl. Irregular sausage-shaped mass palpable in right iliac fossa. X-ray barium series shows persistent narrowing of the terminal segment of ileum.

*Operation (27.11.47).*—The terminal 8 inches of ileum were greyish in colour with some small tubercles on its surface. The width of the bowel was normal, but the lumen felt grossly narrowed by thickening of the wall. On palpation the bowel felt like an unpliant tube of rubber. It was twisted on itself and bound to its own mesentery and to a further loop of ileum 18 inches proximally. This latter area was also thickening, and after separation of adhesions it appeared as a "skip" area. The mesentery was grossly thickened and oedematous and contained enlarged lymph nodes. Resection was carried out to include both affected segments of ileum along with ascending colon, and proximal ileum and transverse colon were anastomosed side-to-side.

*After History.*—Patient made a good recovery. Bowels were loose at first, but a year later were moving daily and she had put on 14 lb. in weight. She has now emigrated to South Africa.

*Pathological Examination.*—Macroscopic as in Fig. 9. Microscopic: the mucous membrane is ulcerated and covered with pus and cell debris.

The submucosa (Fig. 3) is infiltrated with chronic inflammatory cells, and there are several foci of reticulocytes with a few scattered giant cells. The muscle and other coats show collagenous fibrosis.

### ÆTIOLOGY ; WITH DISCUSSION

The ætiology of regional ileitis is at present not known, though the ulcerative and inflammatory changes are such marked features that at first sight the condition would appear to be due to infection by some organism. No specific organism has been identified, however, and a wide selection of ætiological factors have been put forward to account for the lesion. It has been variously suggested that the disease is due to :—

(1) *Anatomical Peculiarities*.—(a) of the ileum ; (b) of its mesentery ; (c) of its blood supply ; (d) of the cæcum, which may be too high ; too low ; too fixed ; too mobile.

(2) *Accidental Causes*.—(a) twisting ; (b) angulation ; (c) intussusception, partial and intermittent ; (d) volvulus ; (e) impaction of a foreign body, such as a fish bone, beneath the mucous membrane.

In none of the cases of ileitis that I have seen was there anything in the nature of a primary anatomical or mechanical abnormality that might have initiated the subsequent inflammatory changes. It is of course difficult to assess what was the original state of affairs when one is confronted at operation with an ileum that is rigid and stenosed, a mesentery œdematous and contracted, and a cæcum surrounded by adhesions. In the absence of evidence to the contrary, it is reasonable to assume that these changes are secondary to the inflammation in the bowel, and are not themselves primary features.

In the acute cases of ileitis that I have operated on there were no features, such as an undescended cæcum, that struck me as being primary defects. The terminal ileum was inflamed and œdematous, and it looked not unlike what one might expect to find in a self-reducing ileo-colic intussusception. Nevertheless one feels instinctively at operation that this is not a reduced intussusception. If an intussusception was the underlying factor in this disease, it is certain that more visual proof of it would have been obtained in one of the several hundred cases of ileitis that have been reported to date.

(3) *Neuro-muscular Causes*.—It has been suggested that neuro-muscular inco-ordination, such as may obtain in achalasia of the lower end of the œsophagus, congenital hypertrophic pyloric stenosis, and in megacolon, may be a predisposing factor and induce ileal stasis, infection, infiltration and finally obstruction. This can only be a hypothesis, for no evidence has been advanced in support of the history. In a true achalasia the characteristic features are spasm at some valve of the gastro-intestinal tract, with dilatation and subsequent hypertrophy of the gut proximally. Ulceration and inflammation are not seen, even in a potentially infective region such as the colon.

(4) *Primary Appendiceal Disease*.—Those who believe that ileitis

follows appendicitis believe that the ileum becomes involved not by surface contact with the inflamed appendix, nor by spread within the lumen of the gut, but by involvement of the mesentery of the terminal loop of the ileum. Bockhus and Lee <sup>7</sup> conceive the possibility of a lymphangitis and surrounding inflammation in the mesentery which might encroach upon or infect the blood supply, producing a slow devitalisation of the terminal ileum and resulting in terminal ileitis. In this view the involvement of the ileal mesentery is the result of spread of infection, either directly from the surface of the appendix or via the meso-appendix.

Against these views is the almost constant finding, when the ileitis is seen at operation, of a relatively innocuous appendix. This has been my experience, as well as that of most other surgeons. In some of Crohn's cases of ileitis the appendix had been removed many years before the onset of symptoms of ileitis.

(5) *Infection of the Ileum.*

(a) *The Common Intestinal Organism.* The many individual organisms of the intestinal tract have been found at times in the wall of resected bowel or associated glands, but there never has been any constancy in the findings. Cultures were made in five of my cases: in two there was a growth of *B. coli*; on one, non-hæmolytic streptococci; and in two there was no growth.

Mixer <sup>8</sup> obtained in two of his less advanced cases an anærobic streptococcus in pure culture from the free peritoneal fluid and from the cut surface of the mesenteric glands. Jackman <sup>9</sup> found streptococci of the intestinal group in the floor of the ulcers. Such organisms, *e.g.* enterococci and streptococcus *fæcalis* were commonly found in the *fæces* of my patients, and it is easy to believe that they might be isolated from an ulcer in the terminal ileum.

Mailer <sup>10</sup> observed that only bacteriological observations made during the acute phase of the disease would be likely to throw any light on the cause of this condition. It has seldom been possible to obtain cultures from the wall of the ileum at this stage because resection is rarely carried out. Mailer reported two cases of acute regional ileitis in which streptococcus *viridans* was isolated on culture, in one case from the blood stream and in the other from the throat. It is recognised that streptococcus *viridans* is capable of giving rise to relatively low-grade inflammation similar to that present in regional ileitis, but further confirmation will be required before it can be regarded as an essential ætiological factor in this condition.

Pumphrey <sup>11</sup> made a careful bacteriological study in thirteen cases at the Mayo Clinic. The organisms most commonly noted were gram-positive and gram-negative bacilli, gram-positive diploci, and gram-positive streptococci, but there was none that could be said to be predominant throughout the series. Many of the organisms recovered were cross-agglutinated with the patient's serum, but positive results were not obtained.

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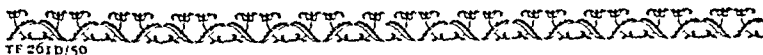
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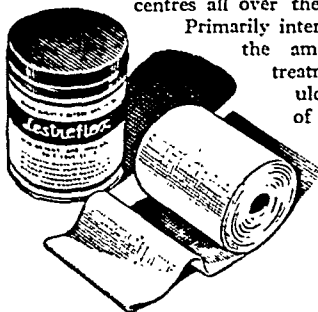
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(b) *Bacillary Dysentery*.—Felsen<sup>12</sup> holds strongly that chronic non-specific ulcerative colitis and regional ileitis are manifestations of bacillary dysentery, and that the ideal therapy is the prevention of dysentery. Felsen followed up a large series of cases of dysentery in America. The terminal ileum was found involved along with the colon in 24 per cent., and in one or two cases the ileitis persisted when the other evidence of dysentery had cleared up.

This evidence is suggestive but not convincing. It is true that not infrequently the ileum is involved in a retrograde manner from an ulcerative colitis, but involvement of the ileum alone has never been regarded by any authorities as a manifestation of bacillary dysentery. I have never been able to recover organisms of the typhoid-dysentery group from the fæces or the resected specimen in my operative material, and neither has Crohn or others who have reported large series of cases of regional ileitis. Bockhus and Lee observe that just as amoebic and bacillary dysentery may eventually cause the same terminal pathological process as the chronic type of ulcerative colitis of unknown ætiology, possibly due to the inroads of secondary invading organisms, so may chronic regional ileitis result from a number of heterogeneous primary irritating factors.

(c) *Tuberculosis*.—For two reasons tuberculosis may reasonably be regarded as the cause of this condition at the lower end of the ileum. Firstly, this has generally been regarded as a common site for tuberculosis of the intestine, in the form of a firm mass mostly in cæcum and involving ileum, to which we give the name ileo-cæcal tuberculosis. Such a mass resembles regional ileitis when the ileitis has spread to involve cæcum; but in ileitis the characteristic firm unyielding length of several inches of terminal ileum is quite dissimilar to ileo-cæcal tuberculosis, and to the short strictures of tuberculosis of the ileum. The presence on the serous surface of small tubercles is not diagnostic of either disease, since in advanced cases of ileitis localised patches of fibrosis, or focal collections of lymphocytes, may be seen. Nevertheless surface tubercles are commoner in tuberculosis, and they are not commonly seen in ileitis.

Secondly, in the microscopic section of the resected bowel in some cases of regional ileitis typical and atypical "tubercles" are seen. These consist of whorls of mononuclear cells, endothelioid cells and giant cells, and it is not easy in their presence to deny the possibility that the condition really is tuberculous. It should be borne in mind however that tubercles in the wall of the intestine are not pathognomonic of the disease caused by the tubercle bacillus; they indicate a reaction to a foreign body or organism. The tubercles that I observed microscopically in three of my cases of ileitis differed slightly from the characteristic tubercles of tuberculosis in that there was never any suggestion of caseation, and the nuclei of the giant cells were usually irregularly placed. The multinucleated giant cells are said very frequently to contain particles of a crystalline or lipid nature which

undoubtedly represent food remnants. Coffey<sup>13</sup> in a study of these aspects at the Mayo Clinic found that true tubercles, with the endothelioid reaction, central caseation and giant cells, were encountered only in material from patients who had active pulmonary tuberculosis.

In Hadfield's study of the pathological process he could find no positive evidence for tuberculosis, but he mentions that the lymphadenoid hyperplasia of the submucosa is a picture that could be caused by the lipoid of dead tubercle bacilli. Taylor<sup>14</sup> suggested that a chronic tuberculous lymphangitis of the mesentery may be the basis for many cases of regional ileitis. His evidence rested on three cases of ileo-cæcal tuberculosis which resembled regional ileitis, but which later showed unequivocal signs of tuberculosis elsewhere. None of my cases have shown any clinical or radiological evidence of tuberculosis, and the same may be said of the vast majority of reported cases of regional ileitis.

Histological distinctions are not final, however, and it is in such cases of ileitis, with tubercles seen microscopically, that the additional tests of specially stained sections and guinea-pig inoculation are of particular value. In none of my cases was the tubercle bacillus seen in sections stained Ziehl-Neelsen, and, most important of all, guinea-pig inoculation with material from the wall of the ileum was negative for tuberculosis in the four cases in which the test was tried. Guinea-pig inoculation has not been carried out so extensively as it should, but where it has been done the findings correspond with my own. Pumphrey<sup>11</sup> did guinea-pig inoculation tests in eleven cases of regional ileitis. In only one was it positive, and this was a granuloma of the ascending colon in which the pathological picture was that of tuberculosis.

The weight of evidence, therefore, is heavily against the tuberculous theory of origin; whereas Boeck's sarcoidosis, with which regional ileitis has been compared, probably is a manifestation of tuberculosis.<sup>15</sup> Boeck's sarcoidosis and regional ileitis have a similar histological picture, but otherwise the conditions seem quite distinct. Morland<sup>16</sup> did report a case of sarcoidosis of the lung with regional ileitis; but apart from such an isolated case, there is no evidence that the two diseases, with such widely different clinical features and such dissimilarity in the distribution of the lesions, have the same ætiological basis.

(6) *Other Rare Infections and Processes*.—Several rare conditions may be mentioned only to be dismissed.

*Syphilis*.—The Wassermann reaction was negative in all my cases. Spirochætes have never been demonstrated in regional ileitis by several workers who have searched for them.

*Actinomycosis*.—The persistent sinuses and the granulomatosis resemble actinomycosis, but the streptothrix has never been demonstrated.

*Hodgkin's Disease and Lymphosarcoma*.—In its histological picture regional ileitis does not resemble these two conditions.

(7) *Food Allergy*.—It is suggested by some workers that an allergic tendency might account for ileitis. Dixon,<sup>2</sup> with a large experience of regional ileitis, mentions that many of his patients were found to be sensitive to whole milk. The evidence in favour of food allergy is slight but cannot yet be dismissed, and there may be some connection between regional ileitis as we know it and the non-specific mesenteric adenitis seen in children, which in turn is possibly due to a localised enteritis in the terminal ileum.

(8) *Virus Disease*.—In the absence of other ætiological factors it is customary in diseases of unknown origin to fall back upon ultra-filterable viruses as a possible cause. There is a certain amount of justification for doing so in regional ileitis because a not dissimilar granuloma of the colon, secondary to lymphogranuloma inguinale, is indeed caused by a virus. I have applied the Frei test to three of my cases, with negative results, and this was also Stafford's<sup>17</sup> experience. This did not surprise us, for we did not expect that the virus of ileitis (if there is one) is the same as the virus of lymphogranuloma inguinale.

Certain experimental work of my own—to which I shall not allude here—has a bearing on this question. At the moment it must be said that there is no evidence that regional ileitis is caused by an ultra-filterable virus.

In concluding a review of the ætiology of regional ileitis, one is forced back to the view that Crohn put forward when he first described the condition in 1932: "The ætiology of the process is unknown; it belongs in none of the categories of recognised granulomatous or accepted inflammatory groups." Hadfield's suggestion that the primary change is in the lymphoid follicles of the submucosa favours a toxin theory. But the majority of workers feel that it is an infection of some sort, the organism gaining access through a breach in the mucous membrane and spreading to the intestinal wall, with œdema of the mesentery from inadequate lymphatic drainage.

#### RELATIONSHIP OF REGIONAL ILEITIS TO OTHER BENIGN INTESTINAL PROCESSES

I want to return to the question about the "newness" of regional ileitis, and I would like to know: (a) Is this a condition which, if not new, is at any rate being seen more frequently nowadays? (b) What label was applied to similar conditions in the past? and (c) Is there evidence that this really is a separate entity from, for example, ileo-cæcal tuberculosis.

There exists in the medical literature a heterogeneous group of benign intestinal lesions which have now and then been described under the caption of "non-specific, or benign, granuloma." The term covers a multiplicity of conditions in which both large and small intestines may be involved; it includes all chronic inflammatory lesions of the intestine whose ætiology is either unknown or attributable



to an unusual physical agent. It represents a melting-pot in which are thrown all those benign inflammatory intestinal tumours which are neither neoplastic nor due to specific bacterial agent, and which are recognised as not being carcinoma, lymphosarcoma, tuberculosis, syphilis, Hodgkin's disease, or actinomycosis.

Within this group we find descriptions of foreign body tumours, chronic perforating lesions with gross inflammatory reactions, trauma of the mesentery with intestinal reactions, a late productive reaction to released strangulated hernias of the intestinal wall, and numerous other and similar conditions.

These non-malignant tumours were most frequently reported as occurring in the colon. In 1907 Moynihan<sup>18</sup> wrote in the *Edinburgh Medical Journal* on "The Mimicry of Malignant Disease in the Large Intestine." The six cases he reported involved the distal colon and were probably due to diverticulitis. Mayo-Robson<sup>19</sup> in 1908 described five similar tumours of the colon which proved to be inflammatory, and he believed that the pathology in these cases was "a chronic infiltrating colitis, possibly associated with pouches lodging faecal matter, or simply due to infection spreading through the intestinal walls."

Not all these granulomata were described as in the colon however, and as far back as 1813 Combe<sup>20</sup> reported "a singular case of stricture and thickening of the ileum," and Moore<sup>21</sup> in 1882 reported "Stricture of the intestine at the ileo-cæcal valve." These cases might be acceptable to our standard of regional ileitis, and certainly when in 1913 Dalziel<sup>22</sup> wrote on "Chronic Interstitial Enteritis" he appears to describe a similar lesion.

Dalziel was drawing attention to a condition which he felt had not been fully described, and to which he gave the name Chronic Interstitial Enteritis. In one remarkable case of a doctor with intestinal obstruction "the whole of the intestines, large and small alike, were contracted and rigidly fixed, so that when a loop was lifted from the abdomen it sprang back into its sulcus. That the whole of the intestine was chronically inflamed there was no doubt . . . the glands were enlarged." Whatever may be thought of that case the two other cases that Dalziel described are almost identical with our conception of regional ileitis. In one a portion of jejunum, over two feet in length, was rigid and thickened; in the other a loop in the middle of the ileum was apparently acutely inflamed. Both these specimens were excised, and the one showed the regenerative process in the ascendancy, with young granulation tissue spreading through the coats of the bowel; and the other showed the acute phase with hæmorrhages, œdema, and areas of necrosis in the mucous membrane, and infiltration of all coats with polymorphonuclear leucocytes. He noted that the lymphoid aggregations were singularly free from pathological change.

Moschcowitz and Wilensky,<sup>23</sup> in 1923, reported a very suggestive case of a young man of 23 who for two years had complained of

cramp-like abdominal pains and of diarrhoea, and had lost weight. At operation the cæcum was found to be the seat of a firm mass. A local resection was done, and a fæcal fistula persisted after operation until it was closed by a second operation a year later. Thereafter he continued to have diarrhoea until, after several bouts of cramp-like pains, he was admitted to hospital in an attack of acute intestinal obstruction. Again he was operated on, and this time it was found that the terminal foot of the ileum was grossly thickened and stenosed, and its mesentery was oedematous. The affected portion was excised, and the patient got well. The macroscopic and microscopic appearance of the affected cæcum and ileum was exactly that which we observe in regional ileitis. Cross-section of the ileum showed an immense thickening of all the coats of the gut so that the lumen was merely a bare slit. The mucosa was intensely inflamed and showed areas of ulceration. The submucous and muscular layers were almost entirely replaced by granulation tissue and throughout all the layers there was a marked infiltration with polymorphonuclear leucocytes and small round cells. Giant cells were abundantly scattered through the wall, many of them containing vague foreign body fragments whose nature was uncertain. In view of the modern tendency to widen the scope of regional ileitis, and include associated lesions in the cæcum and jejunum, this case corresponds strikingly with our conception of Crohn's disease.

Moschcowitz and Wilensky, from further studies, concluded that many, if not the majority, of the examples of so-called "hyperplastic tuberculosis of the colon" are really simple granulomata. They cite characteristic quotations from the literature on hyperplastic tuberculosis of the intestine: Lartigau says "more often the tubercles are mere aggregations of lymphoid cells in which one or more giant cells are seen. Epithelioid cells are usually absent. Many show little tendency to necrotic change; a distinct tendency to fibrous transformation is apparent. The typical histological features of tubercle bacilli are often absent." Ignard says, "In many cases of hyperplastic tuberculosis of the intestine no tubercles, giant cells or bacilli are found. The lesion is constituted of a mixture of variable proportions of tuberculous and inflammatory elements. In certain cases, the last only exist." Doubt seems to have crept into the mind of but one observer, Richter. He believed that hyperplastic tuberculosis is really a non-specific inflammation of the cæcum, and that the tuberculosis is only an accidental infection and complication, the result of swallowing tubercle bacilli either from a pulmonary focus or in milk.

Erdman and Burt<sup>24</sup> summarise the modern views on the formation of these granulomata. They believe that, though the ætiological factor in these cases may not be known, it is probable that there is first an interruption in the continuity of the mucosa as a reaction to the presence of an infectious or toxic agent or an indefinite foreign body, resulting in ulceration of the mucosa. With the destruction of the

mucosa active infection follows, and extends into the walls of the intestine, setting up a low grade inflammatory process, which manifests itself in the cellular infiltration and connective tissue formation, which constitute these granulomata.

As a further line on possible masquerade of regional ileitis in the past I thought it might be enlightening to examine certain medical records at the Edinburgh Royal Infirmary. Some of these cases of regional ileitis that I have described were in the charge of the late Sir David Wilkie when I was his Clinical Tutor. During his period as a Surgeon to the Royal Infirmary, from 1925 to 1938, Professor Wilkie had charge of 12,000 cases, and these included a considerable proportion of abdominal cases, in which branch of surgery Professor Wilkie was particularly interested. From these 12,000 cases I have separated 63 which are relevant for discussion as involving ileum, cæcum, or both.

The diagnosis attached to these 63 cases was :—

<i>Ileum (alone)</i>	<i>Cæcum (alone)</i>	<i>Ileum and Cæcum</i>
Tuberculosis . . . 7	Carcinoma . . . 16	Tuberculosis . . . 8
Carcinoma . . . 5	Tuberculosis . . . 5	Carcinoma . . . 7
Regional Ileitis . . 5	Typhlitis . . . 4	Regional Ileitis . . 1
Stricture of ileum . . 1	Simple ulcer . . . 3	
Ileal fistula . . . 1		

Wherever possible I myself have made a fresh examination of the microscopic section from these specimens, using the same standards as for the recent regional ileitis cases: and where the section is no longer available I have assessed them from the original report. Thus I find that all the cases of carcinoma had the microscopic criteria of malignancy.

The examples of regional ileitis are those that I have already described. All have occurred since 1936.

The stricture of ileum was thought to be typhoid in origin.

The ileal fistula was in an old man who had had an abdominal fæcal fistula ever since an operation 22 years previously—possibly for Meckel's diverticulum. When Professor Wilkie closed the fistula there was nothing abnormal to be seen apart from the communication with healthy low loop of ileum.

The four cases of typhlitis were all associated with appendicitis. It is certain that a degree of thickening or inflammation of the cæcum in association with a true appendicitis must have occurred in more than four cases, but it had not been thought necessary to classify such as typhlitis. In none of these four cases was there any comment on the state of the ileum, which was presumably not the site of obvious disease.

Simple non-specific ulcer of the cæcum is a rare but well recognised condition. It is situated on the anterior wall of the cæcum or opposite to the ileo-cæcal valve. The ætiology is unknown, and there is a

tendency to link them up with ulcers elsewhere in the gastro-intestinal tract.<sup>25</sup> They frequently perforate, but there is no evidence that they ever go on to form a granuloma that might be mistaken for regional ileitis.

The 22 cases of tuberculosis were interesting. I had thought that it might prove difficult to differentiate them from regional ileitis. In point of fact 18 of them presented quite a different picture from regional ileitis: there were clinical differences, and differences in the distribution of the lesion, multiple strictures of the ileum, and caseation in the tubercles and other features. In four cases, however (two cæcal and two ileo-cæcal tuberculosis) the diagnosis was open to question, and depended principally on the belief that because tubercles are seen microscopically the condition must be due to the tubercle bacillus. Bacteriological and inoculation tests had not been done in these cases and therefore I am unable to say that they were not tuberculous.

I have, from this study of Professor Wilkie's 12,000 cases, been unable to find any evidence that regional ileitis has been going unrecognised or misinterpreted. It is possible that a search of the records of the 1500 cases of appendicitis that helped to make up the total of 12,000 might have shown that ileitis in its acute form had been noted. This is unlikely, because so gross a lesion as acute ileitis would almost certainly have drawn attention to itself and received classification.

One is sometimes asked by pathologists: "How, if this is a new disease, is it that we are not encountering it in the post-mortem room?" The answer may be that it is a disease principally affecting young people, and either they have not died of it or they have had their affected bowel resected. In spite of a natural disinclination to accept new diseases there can be little doubt that regional ileitis is occurring more frequently than it did, for example, 36 years ago when Dalziel described two cases of "chronic interstitial enteritis," or even 136 years ago, when Combe described his "singular case of stricture and thickening of the ileum." Sir David Wilkie said to me, when on one occasion we discovered a regional ileitis at operation:—"This is not a condition that we used to see. I have been operating on the abdomen since early this century and I am sure I would have taken note of such a distinctive appearance if it had been occurring. This is something quite different." Sporadic cases may have occurred, but nevertheless full credit must go to Crohn and his co-workers for so brilliantly separating this condition, with its well-defined clinical and pathological features, from the confused collection of non-specific intestinal granulomata.

#### SUMMARY

1. The clinical and pathological features of regional ileitis have been described.

2. The ætiology of the condition and its relationship with other intestinal granulomata, has been discussed.

3. Eight personally observed cases of regional ileitis are presented.

4. Study of these cases has thrown no further light on the ætiology of the condition, which remains unknown. Guinea-pig inoculation and other tests for tuberculosis were negative, which adds weight to the belief that regional ileitis is not a form of tuberculosis.

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## CHEMOTHERAPY IN RETICULOSIS

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IN the course of an hour's lecture one can only hope to touch on a very few aspects of so large a subject as chemotherapy in reticulosis. It is, however, a field of medicine of tremendous importance and one in which the pace of progress in recent years has brought such challenging achievements that everyone connected with medicine should know at least a little of what is going on.

In its broadest sense the term "Reticulosis" means an affection of the reticulo-endothelial system, that widespread family of heterogeneous cells, all with a common mesenchymal ancestry, but highly specialised for many vital functions ranging from defence mechanisms against infection, to bile pigment formation, and the production of all the formed elements of the blood. Affections of this system are diverse and include varying types of cellular reaction to infective processes and abnormalities of storage such as the rare lipoid storage diseases. However, in recent years the word "Reticulosis" has come to be applied more and more to the neoplastic conditions that involve primarily the reticulo-endothelial tissues. Many clinicians use the term somewhat loosely to describe a whole group of such diseases, which they regard as difficult to classify, and which when diagnosed are referred as such to the province of radiotherapy for treatment. Those who have interested themselves in this most important group have learned that their classification on histological grounds is a complicated and highly specialised study, and it is the radiotherapists, who have dealt with the cases for treatment over the past twenty years, who have contributed mainly to the present understanding of their varied clinical aspects. It is now recognised that while, as neoplastic diseases, the reticuloses are all eventually fatal, they differ greatly in their presenting features, in their rate of progress and in their response to radiotherapy. They may be localised or generalised in the reticulo-endothelial tissues, and may, or may not be associated with a leukæmic change in the marrow and/or peripheral blood. It is the tendency of one clinical type to merge into another, which is the confusing issue when attempting a purely clinical classification, though on histological grounds this is much easier to understand. It is, however, important to recognise that some of these malignant conditions progress so slowly that they do not necessarily shorten life and that many patients with reticulosis can be maintained in excellent health for many years by X-ray therapy.

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There are several reasons why treatment by drugs has been sought after as an alternative to radiotherapy. The latter is a highly technical field calling for specialised staff working with expensive apparatus in selected centres, to which patients may have to travel long distances for treatment. It is recognised that some reticulososes, while responding initially to X-rays, develop in time intolerance to further radiation and other cases show little response from the outset. The development of intolerance is understandable when it is realised that the rays are essentially unselective agents which inhibit the growth of all actively growing tissues and as such are bound eventually to suppress normal hæmopoiesis to a degree when further dosage is injurious to the general health of the patient. There seems to be a marked individual variation in this respect, and often the continued treatment of a neoplastic process may have to be abandoned because of the onset of marrow hypoplasia. Radiation sickness is another unpleasant side effect which may cause much distress to a patient already ill. The use of radioactive isotopes has not materially overcome any of these disadvantages and the need for alternative means of treatment by chemotherapy, having possibly a more selective action on abnormally growing cells, has grown ever more apparent. A great amount of research towards this end has gone on for many years, with many hopes and bitter disappointments, and although to-day the answer still seems a long way off, there have emerged in recent years some compounds of great interest which appear at least to represent a step in the right direction. It is with a few of these drugs that this lecture is concerned and it will be convenient to deal with them separately and to illustrate their action in the treatment of some of the more important reticulososes encountered in general clinical medicine.

#### ARSENIC

The use of this metal in the treatment of leukæmia was advocated as long ago as 1865 by Lissauer and it is thus the oldest form of chemotherapy for such conditions. Interest in its effects was revived by Forkner and Scott in 1931 and since then a number of workers have tried to establish its mode of action. Hunter, Kip and Irvine (1942), showed that when radioactive sodium arsenate is given to man, it can be demonstrated in the cells of the peripheral blood with a concentration in the leucocytes ten times greater than in the erythrocytes. In studies of human marrow cell respiration, Warren (1943), found that arsenic depressed this function. Piney (1948), believes that arsenic can decrease the rate of reproduction of early precursor cells of the myeloid series. Whatever its mechanism of action, there seems little doubt that in some cases of chronic myeloid leukæmia, arsenic therapy can bring about a profound fall in an abnormally high leucocyte count, accompanied by a decrease in splenic enlargement and improvement in hæmoglobin level and general state of health. The metal is administered in the form of Fowler's solution of potassium

arsenite according to a dosage schedule recommended by Forkner and Scott (1931). Maintenance dosage has often to be stopped on account of peripheral neuritis or dermatitis. Arsenic has been found to offer no benefit in cases of acute leukæmia and is of little help in the treatment of chronic lymphatic leukæmia. Its greatest value is in the chronic myeloid group, and particularly in cases which are responding poorly to X-rays, as its action does not seem to be affected by previous radiation. The white blood-cell count tends to rise again within three weeks of stopping the drug. There are several authorities to-day who maintain that arsenic has still a definite place in the treatment of leukæmia and that it is well worthy of trial and further investigation.

#### URETHANE

This simple chemical compound, ethyl carbamate, was first introduced as a chemotherapeutic agent in leukæmia by Haddow and his co-workers in 1946. They reported the results of treatment in 32 leukæmic cases, finding that in approximately one-third of the patients the drug was effective in reducing the size of the spleen and lymph nodes and in reverting the blood picture to a more nearly normal appearance. The urethane effect was roughly equal in value to that of standard X-ray therapy given to a control series of similar cases. They noted that the cases of chronic myeloid leukæmia benefited most, with clinical and hæmatological remissions maintained for periods of two to six months. The drug was administered orally and toxic side effects observed included nausea, drowsiness, anorexia and diarrhœa, and marrow hypoplasia occurred in two cases of their series.

Since then several reports have appeared in the British and American literature of clinical trials with urethane in cases of leukæmia. In a total of nearly 150 patients the observations of Haddow have been confirmed and it may be concluded that the drug is a satisfactory therapeutic agent in producing temporary remission in chronic myeloid and occasionally in chronic lymphatic leukæmia. It is of no value in acute leukæmia. Whether the duration of life of such patients will be significantly prolonged is not yet established, as this will require much longer follow-up than has been possible to date. The drug has advantages over some forms of therapy in that it is inexpensive and easy to administer, but it is extremely nauseating to many patients and is potentially dangerous since it can produce marked depression of function of the normal elements of the bone marrow. The initial dosage of urethane in cases of leukæmia is 1.0 gm. given thrice daily, by mouth, in syrup of orange and chloroform water. Nausea occurs in about 50 per cent. of cases, but the daily dosage can if necessary be increased slowly to 5.0-7.0 gm. In cases of chronic myeloid leukæmia with a very high leucocyte count, a total of 90-100 gm. of urethane, given over about thirty days, is the



average amount required to reduce the count to around 20,000 per c.mm. Thereafter the drug can be continued in low doses as maintenance therapy, *e.g.* 1.0-2.0 gm. daily if well tolerated, but dosage must be carefully controlled in each case by repeated blood examinations, and a watch kept for signs of commencing marrow hypoplasia.

Urethane has also been found of value in the treatment of multiple myeloma, a disease in which many different types of therapy have failed to alter significantly the clinical course of the condition. Although reports of clinical trials with urethane are few, and the earlier results seemed disappointing, more recent work by Loge and Rundles (1949), is much more encouraging. They treated 4 patients with multiple myeloma for eight to ten weeks with total doses of 120-190 gm. and observed the cases for periods of from seven to thirteen months. Striking benefit relating to all aspects of the disease was noted with marked clinical improvement and a decrease in the number of abnormal plasma cells in the bone marrow. A most interesting feature was a return to a more normal pattern of the serum protein abnormalities characteristic of this disease. The progress of destructive lesions of the skeleton seemed also to be arrested, though little evidence of bony recalcification was evident six months after treatment. Further work will be necessary to establish the value of urethane in the long-term therapy of multiple myeloma, but it does seem capable of relieving the more active features of the condition and as such marks a very significant step in the treatment of this disease.

The exact mechanism of action of urethane is not clearly understood. Haddow has suggested that it competes with a natural amine involved in the biosynthesis of nucleotides. It appears that it can interfere with the mitosis of primitive leukæmic cells and Osgood *et al.* (1948), have reported that in cultures of human marrow it causes an aggregation of the nucleoprotein of cell nuclei, especially in cells of the myeloid series. Whatever its actual mode of action, there is evidence that this simple compound can affect the growth processes of certain abnormally proliferating cells, and as such, its introduction has represented an important advance in the wide problem of the chemotherapy of neoplastic disease.

#### NITROGEN MUSTARD

During the recent war years a new approach in this field of chemotherapy was developed in the course of military research on chemical warfare. A group of agents known as the nitrogen mustards, or beta-chloroethyl amines, was found to have a profoundly toxic effect on both normal and neoplastic tissues of the hæmatopoietic system. Much of the basic work leading to an understanding of the action of these mustard compounds was done in Britain by Peters and his co-workers (1940), though, owing to the necessity for secrecy, the drugs became available for clinical trials in America before most people had heard of them in this country. During the past four years

several clinical reports on their use in the treatment of neoplastic conditions have appeared in the American literature.  $\text{HN}_2$  or methyl-bis (beta-chloroethyl) amine hydrochloride, known in Britain as Di-(2-chloroethyl) methylamine hydrochloride, has been found to be the most satisfactory of these compounds for therapeutic use, and the National Research Council of America has recently published a report by Karnofsky (1949) on its use which gives a clear view on its value in the light of present knowledge. The summary of this report is quoted as follows :—

“Nitrogen mustard represents a new and valuable agent for the management of inoperable neoplastic disease. Methyl-bis (beta-chloroethyl) amine hydrochloride ( $\text{HN}_2$ ), the nitrogen mustard in clinical use, is a systematically acting cell poison most closely related in its therapeutic effects to total body irradiation. Its advantages over total body irradiation are that it is less expensive, easier to administer, its toxic and therapeutic effects develop more quickly, tissue recovery is more rapid and its dosage can be more safely controlled, so that maximum therapeutic doses are possible. Total body irradiation causes less nausea and vomiting and its therapeutic effects may be more prolonged.  $\text{HN}_2$  is an effective, temporary, palliative agent of irregular activity in Hodgkin's disease, lymphosarcoma, chronic leukæmia, polycythæmia vera, mycosis fungoides, primary lung carcinoma, and, to a much lesser degree, in other miscellaneous neoplastic disorders. There is little evidence, however, that it alters the course of these diseases or appreciably prolongs life. Its great value is as an adjuvant to X-ray therapy in the palliation of neoplastic disease. X-ray therapy is more effective in treating localised disease. . . .  $\text{HN}_2$  should be given only when definite indications exist. Because of its toxicity and unpleasant side effects, its indiscriminate trial in patients with inoperable cancer, or in the terminal stage of the disease, is entirely unjustified.”

The above report was based on a review of clinical trials carried out in several American centres and similar results have recently been obtained with nitrogen mustard in this country. There seems little doubt that the drug is especially useful in the treatment of Hodgkin's disease, particularly in severe cases with marked constitutional symptoms and visceral involvement. In these cases, a period of complete rehabilitation and a definite increase in life span of from two months to two years may follow the use of one or several courses of nitrogen mustard. These and other conclusions relating to its effect in Hodgkin's disease are discussed by Dameshek, Weisfuse and Stein (1949), who report on 50 cases treated and observed since 1942. Nitrogen mustard appears to have an almost specific affinity for the abnormal tissues of Hodgkin's disease and although it is a chemical without any radioactivity, its effects resemble closely those of X-rays. It is, however, often capable of producing complete remissions in cases that have proved refractory to continued X-ray therapy, and it is claimed that a return to radiosensitivity, may in some cases, follow the use of a course of nitrogen mustard. The above authors still consider that in the early stages of Hodgkin's disease, radiotherapy is

the treatment of choice as it usually offers longer remissions than can be obtained with mustard. They suggest that a combination of X-ray and mustard therapy may be found to be the best way of dealing with the majority of cases of all clinical types.

The dosage of nitrogen mustard recommended is 0.1 mgm. of Di-(2-chloroethyl) methylamine hydrochloride per Kgm. of body weight administered on successive or alternate days with a total of 3-6 injections. The maximum single dose employed should not normally exceed 8 mgm., but if an initial amount of 4-5 mgm. is well tolerated, succeeding doses can be increased by 1 mgm. at a time. The most satisfactory technique for giving the drug is to add 10 ml. of 0.9 per cent. sterile solution of saline to 10 mgm. of the dry salt and to inject the required amount of the freshly prepared solution into the rubber tubing of a freely flowing saline, intravenous infusion. Thrombosis and severe local reaction are liable to result from any extravasation outside the vein. The great majority of patients experience nausea and vomiting, beginning one to six hours after the injection and lasting for two to four hours, and many have rigors. A marked fall in the lymphocyte count may precede profound leucopenia, which is an indication for suspending treatment, and thrombocytopenia with a hæmorrhagic tendency may also occur. It is not advisable to administer courses of mustard therapy at intervals of less than six to eight weeks.

The powerful cytotoxic effect of nitrogen mustard appears to take place within a few minutes of its intravenous injection. Peters and his colleagues (1940), believed that the action was due to interference with essential intracellular enzymes, but subsequent workers, Morowitz *et al.* (1946), Stahman and Stauffer (1947), and Friedenwald and Buschke (1948), have shown that the chemical is mainly an inhibitor of mitosis, which is the biological duplication process of structures rich in nucleic acid. Nitrogen mustard can cause mutations in chromosomes by interfering with their nucleic acid structure, and in very low concentrations, can inhibit the normal synthesis of cellular nucleic acid. The resting stage of the mitotic cycle appears to be the most sensitive period to the action of the chemical, which in high concentrations can produce nuclear fragmentation and abnormal chromosomal patterns transmissible through succeeding generations of cells. These effects of nitrogen mustard very closely resemble the action of X-rays. That the fundamental growth processes of certain neoplastic cells can thus be adversely influenced by a chemical agent, is again another real step forward in the therapy of malignant disease.

#### STILBAMIDINE

An interesting development in the chemotherapy of reticulosis, has been the use by Snapper (1946 and 1947), of stilbamidine and pentamidine in cases of multiple myeloma. His rationale for trying these drugs was based on the fact that in both myelomatosis and

kala-azar, there is a marked elevation of blood globulins, which in the latter disease are lowered by stilbamide therapy. Snapper showed that following treatment of patients with multiple myeloma with this drug, relief of bone pain could often be obtained and that large, basophilic, inclusion bodies appeared in a high percentage of the myeloma cells in the marrow. He noted that these inclusion bodies were found only in patients who had hyperglobulinæmia and Bence-Jones proteinuria and who were taking a low protein diet, and that they did not occur when pentamidine was used in treatment. The inclusion bodies contained ribose nucleic acid, and in a patient who died eight days after a course of stilbamidine, the drug was found by analysis in myeloma tissue at post mortem. Snapper advanced the theory that stilbamidine reacts specifically with the cytoplasmic nucleoproteins of myeloma cells and that a high protein diet may interfere with this reaction. He suggested that the relief of bone pain is due to an arrest of myeloma cell proliferation, although he was unable to show any decrease in the percentage of these cells in marrow smears during or after treatment. This hypothesis is interesting when correlated with the work of Kopac (1945), who showed that stilbamidine may act on nucleoproteins *in vitro* with the release of protamines from protamine-ribonucleate complexes and the simultaneous binding of nucleic acids. It seems possible that the nucleoproteins of neoplastic cells are more readily dissociated by stilbamidine than those present within normal cells.

Stilbamidine is administered by either intravenous or intramuscular injection, the latter route being somewhat painful, so that 2 per cent. procaine should be added. The drug must be in freshly prepared solution and the daily dosage recommended is 150 mgm. continued for three to six weeks. Toxic reactions are common and may occur both immediately, in the form of a syncopal attack, or as a late effect some two to five months after dosage, with toxic degeneration of the sensory nucleus of the trigeminal nerve. The latter disturbing manifestation, producing dissociated anæsthesia of the facial area, occurred in 10 patients out of 18 treated by Arai and Snapper (1947), and persisted for a considerable period before diminishing spontaneously.

Snapper has made no claims that stilbamidine prolongs life in multiple myeloma, or alters the course of the disease, apart from palliative relief of bone pain. Much interest has been caused by his observations which have been repeated by other workers, although detailed studies on the serum of patients with kala-azar and multiple myeloma have revealed fundamental differences in the serum proteins in these two conditions which make the use of stilbamidine in myeloma seem even more empirical than Snapper's rationale for first trying it. Since there is ample evidence that the essential pathology of multiple myeloma is not significantly altered and that the abnormal serum protein patterns persist unchanged after therapy, recent reviewers of this work, Gellhorn and Jones (1949), conclude that stilbamidine

merely provides symptomatic relief in some cases, although its use for this end may be justified as a last therapeutic resort. Its toxicity on the trigeminal nerve and the need for its protracted and painful administration are other drawbacks which weigh heavily against its indiscriminate use in this disease.

### FOLIC ACID ANTAGONISTS

Since the synthesis of folic acid—pteroylglutamic acid—numerous chemical analogues of this compound have been prepared, and a number of them have been found to be potent in their ability to antagonise the growth-promoting properties exerted by folic acid on cultures of *Streptococcus faecalis* R. The two types of analogues of most interest are those in which the components of the pteridine ring of folic acid are either changed or have other groups added, and those in which, in addition to these alterations, the glutamic acid is substituted by another amino acid. In the course of clinical trials of the treatment of a variety of incurable neoplastic conditions with a folic acid conjugate, pteroyltriglutamic acid, Farber *et al.* (1948), gave this compound to 11 children with acute leukæmia. They noted what they described as an "acceleration phenomenon" in the progress of the condition, with very rapid extension of the disease in the viscera and bone marrow. Heinle and Welch (1948), reported that a rapid hæmatological and clinical relapse occurred in 3 cases of chronic myeloid leukæmia given large doses of folic acid, and conversely that by producing a folic acid deficiency in two further patients with this disease, a clear-cut remission resulted, lasting over one hundred days. Such evidence that folic acid and its conjugates could induce an apparent stimulation of abnormal leucocyte production in the bone marrow, led to the hypothesis that folic acid was an essential metabolite for leucopoiesis. It was with this rationale that trials with folic acid antagonists were instituted in cases of acute leukæmia.

Reports on the use of folic acid antagonists in the treatment of leukæmia have come from American workers in the past year. Farber (1948 and 1949), and Dameshek (1949), have published preliminary results in a total of over 60 children and 31 adults. Of several analogues used, 4-aminopteroylglutamic acid (aminopterin), has proved to be both the most effective and the most toxic; so toxic in fact, that its widespread clinical use, without the most careful hæmatological control, appears highly dangerous. While it is generally agreed that at present it is too early to assess the results, it seems that in patients with acute leukæmia treated for three weeks or longer with aminopterin, a well-defined clinical and hæmatological remission is obtained in a third to a half of the cases. The authors make no claims to have induced anything other than temporary remissions in the disease as there is no evidence which would justify the use of the word "cure" of acute leukæmia. Throughout the remissions the leukæmic process has remained recognisable by studies of marrow smears and peripheral

blood. Despite this, Farber (1949), reports the cases of two children whose acute leukæmia is still under control twenty-three months and sixteen months after onset, and Dameshek has patients who have had continued or intermittent remissions up to eight and a half months. The impression has been gained that the best results were obtained in the lymphoblastic cases which were running a relatively subacute, rather than a fulminating course. All the cases were given antibiotics, blood transfusions and other measures whenever indicated in addition to the folic acid antagonist. It is concluded, however, from a careful study of the natural course of acute leukæmia and of the results obtained after all means of treatment formerly employed, that the prolonged remissions obtained after aminopterin have been attributable to the action of this drug, and that it truly indicates a well-defined therapeutic advance.

In Edinburgh, I have been fortunate to have the opportunity of treating cases of leukæmia with aminopterin. While studying the action of this and similar compounds in the United States during 1947-48, a supply of the drug was made available to me, through the courtesy of the Lederle Laboratories, for clinical trial in this country on my return. My series of cases is small, being at present only 15 patients, and the length of the trial has been too short to permit of prolonged follow-up. There are enough findings, however, to permit of a preliminary preview of the use of aminopterin in local hospitals and much fuller data can be published later. Eight adult patients have been treated, six of whom were cases of acute leukæmia and the others chronic. All six of the acute cases died and apart from the possible exception of one patient with the monocytic variety who lasted sixty-four days, I am not convinced that the drug in any way altered the usual rapidly fatal course of the disease. No effects followed the use of aminopterin given for at least four weeks to the two cases of chronic leukæmia and because of these findings and the current opinion in America that this extremely toxic drug produces no benefit in the chronic varieties, I have decided to conserve my limited supply of the compound for cases of acute leukæmia in children. So far 7 children with acute leukæmia have been treated and others are starting treatment. Of the seven, two are alive and receiving maintenance therapy at home five months and four months after instituting therapy, and while the other five have all died, three had remarkable clinical remissions lasting three and a half, four and a half and five months. The two children now at home on maintenance dosage of 0.5 mgm. aminopterin daily, have so far enjoyed full clinical remission with restoration of a normal peripheral blood picture. These are the only two cases of the series that have been kept throughout on daily dosage and it seems probable that the continued administration of small amounts of the drug will prove to have more lasting effect than repeated courses of treatment. All the aminopterin has been given orally, made up in tablets containing 0.5 mgm. of the drug. Treatment

has been started with 1.0 mgm. daily for periods up to five weeks and the children still alive on maintenance therapy have each received total dosage of more than 70 mgm. The drug is extremely toxic and dosage has to be determined in every case on the basis of repeated examinations of the blood and physical condition. Severe stomatitis with buccal ulceration, diarrhoea, gastro-intestinal hæmorrhage, and depression of marrow function leading to anæmia and profound leucopenia are very worrying toxic manifestations that may be encountered during the use of aminopterin, and it is on this account that for the present the widespread use of the drug, other than for research purposes, cannot be entertained. One child, later discharged from hospital with a white blood-cell count of 6600 and a normal differential count, had, at one stage of treatment only one cell, a lymphocyte, to be found in a white-cell counting chamber. In such instances, the use of penicillin and blood transfusions is essential to maintain life. It even seems that the most salutary results are seen in cases where the drug is pushed to the point of distinct and even serious toxicity.

To establish clearly the rôle of folic acid antagonist therapy in acute leukæmia is very difficult at the present time. There is a considerable variation in the results of different investigators, but sufficient evidence is now accumulating to show that in a proportion of cases, especially in children, the period of survival can be significantly prolonged. Any attempt to assess such treatment must be correlated with a study of the natural course of the disease process, and particularly with the recognised occurrence of occasional spontaneous remissions. Apart from lack of knowledge of the essential pathological change that causes leukæmia, there are many other features of the condition, such as the mechanism of hæmorrhage, that remain to be explained, and this is now particularly important as the hæmorrhagic tendency appears to be increased as one of the toxic manifestations of aminopterin therapy. There seems no doubt that aminopterin has an injurious effect on the leucocytes of leukæmia, but there is little differential between its effect on neoplastic as compared with normal cells, and the severe toxic changes which follow the administrations of this and similar compounds, constitute a serious limitation to their wider use.

Irrespective of their ultimate importance in clinical therapy, the folic acid antagonists represent a major step forward in the chemotherapy of human neoplastic disease. Their mode of action is not at present understood, but their effect does not seem to arise specifically from antagonism of folic acid. In support of this there is some evidence that neither the beneficial effect produced in certain cases of leukæmia, nor the toxic manifestations, can be counteracted by the simultaneous administration of folic acid. A possible explanation of their action is that they influence cellular nucleic acid metabolism by modifying various enzyme systems within more primitive cells, but the exact biochemical mechanism on which they may act awaits further elucidation.

## COMBINATION OF RADIOTHERAPY AND CHEMOTHERAPY

An approach to the problem of attempting to improve the treatment of neoplastic disease by the combined use of X-rays and chemotherapy, was suggested by the finding that therapeutic doses of radiation can inhibit the enzyme synthesis of thymonucleic acid in growing cells; Mitchell (1943). The aim in this field is to select a chemical agent able to block the synthesis of nucleic acids by a mechanism different from that of X and gamma radiation, as radiations probably kill cells by producing gross structural changes in the chromosomes during mitosis and this is not directly dependent upon the inhibition of nucleic acid synthesis. Mitchell (1948) has reported the use of a synthetic vitamin K substitute in combination with X-ray therapy in treating 116 cases of advanced tumours, and finds that in large doses, the drug produces a small but useful improvement in palliative results. There are as yet no reports of similar studies in the treatment of reticulosis, but this work is mentioned as it seems to open up a new field of research in the therapy of neoplastic disease.

I have tried to present a few aspects of the possibility of chemotherapy in a group of diseases for which at present no cure is known and the answer to which seems bound up with the problems of the nature, correction and prevention of neoplastic change. There are many studies which indicate that the fundamental difference between normal and neoplastic cells lies in intricate biochemical processes connected with nucleic acid metabolism, on which the division and bodily manufacture of cellular material depend. So far no agent, either physical or chemical, has been found which will sufficiently influence the metabolism of the neoplastic cell without at the same time interfering with cells of normal body tissues. However, within the last very few years, more and more chemicals which affect the vital properties of dividing cells have been discovered. Thus the great mass of evidence, accumulated so laboriously over so many long years, and which has at times appeared so hopelessly diverse and unrelated to the pressing problems, is at last taking on a pattern with cellular nucleic acid metabolism as the most likely centrepiece. I am sure that you are all only too aware of the profound importance of this work—the greatest challenge to medical science still outstanding—and I need scarcely remind you of the utmost restraint required in expecting dramatic results too soon, for in no other line of research is so much wishful optimism to be encountered. I think you will agree, however, that this field of chemotherapy shows signs of much promise and we must all watch for future developments with great and growing interest.

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## "THE FORGOTTEN REPORT"

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Address given to the Southern Medical Society, Glasgow, on 13th October 1949.

THE prodigal wastefulness of Nature enormously impressed our Victorian forbears and has been a subject of speculation by philosophically-minded men throughout the ages. Tennyson, for whom Nature was "red in tooth and claw" remarked also "so careful of the type she seems, so careless of the single life." The fish which lays a million eggs, that one may mature to lay another million eggs, is perhaps the supreme and obvious example. But does not this same habit and tendency extend right into the most sophisticated activities, even of that biologically economical animal, *Homo Sapiens*? Every year thousands of books are published and tens of thousands written. Pictures are painted, statues are hewn, symphonies are composed all over the habitable globe. Like the grass of the field they wither away, and but a handful survive.

Even in the staid and sober realms of the Royal Commission and the Departmental Committee mankind seems to have expressed his thwarted fecundity with reckless extravagance. Far from learning economy he has used his own inventive genius to accelerate and exaggerate this tendency. The late Sir Neville Henderson, Ambassador to Hitler's Germany, in his autobiography recalls that as a young secretary in the Foreign Office he was required to write all notes and memoranda in his own hand, and blames the advent of the typewriter and stenography for much that has happened. I wonder what he would have thought of the latest suggestion that Hansard reporters should be replaced by recording machines!

Whatever be the explanation, the fact remains that, as the production of babies goes down that of committees, commissions and working parties goes steadily up; and something resembling a chain reaction seems to accelerate the process—a thought which prompts the further gloomy speculation that it is perhaps this rather than the other chain reaction which will eventually eliminate mankind in the contest of species on this minor planet!

In current terminology, however, we might regard this as a long-term consideration! Of more immediate interest is the point that this particular kind of production shares the fate of the fish eggs, the poems, the sonatas and the statues. The vaults and storerooms of the civilised world are stuffed with the dusty copies of forgotten reports. It is of a report which is in danger of being, if it has not already been relegated to this limbo, that I wish to remind you this evening, because I believe it to be really important for the future of Scottish medicine that it should *not* be forgotten. Since it commonly bears the name of the

distinguished graduate of Glasgow University who presided over the concluding deliberations of the Committee which produced it, it may be that the Cathcart Report is better remembered here than in other parts of Scotland. I feel, however, that even in Glasgow there may be those whose memories of it are fading. They might be interested to be reminded of some of its principal conclusions and proposals and in a comparison between these and what has ultimately transpired in the form of the National Health Service in Scotland.

A word to begin with about the genesis of the Scottish Health Services or Cathcart Committee. It would, I think, be not far from the truth to say that it was conceived in the fertile mind of that brilliant if unstable genius, the late John Parlane Kinloch—another Glasgow graduate. Kinloch must have been an uneasy team-mate, but whatever one felt about him no one who had dealings with him could fail to recognise the force of the man. He had, I believe, to a quite remarkable degree the capacity to envisage—in an almost physical way—the developments and projects he described, and one had the impression when listening to him that the “mind’s eye” was no mere figure of speech.

In the Annual Report of the Department of Health for Scotland for 1931, when Kinloch was Chief Medical Officer, attention was drawn to the haphazard origin and chaotic development of the multifarious agencies for the prevention and treatment of sickness. To one of Kinloch’s temperament such a state of affairs cried out for remedy. He advocated a complete survey of all the Health Services of Scotland as a basis for future policy and related planning.

The recommendation was adopted and in June 1933 the Committee was appointed by Sir Godfrey Collins, then Secretary of State for Scotland. Three years later, after what was probably the most complete and comprehensive study of its kind, it reported in a document of some 300 pages and 859 paragraphs. The content and tone can perhaps most conveniently be generally indicated by quoting two of these paragraphs.

“ 253. Our findings may be briefly summarised as follows :—

Changes in the size and distribution of the population, in social and economic conditions, in the habits and outlook of the people, and in the actual causes of death and ill-health require a readjustment of health effort. The existing health services are not fully adapted to modern conditions and outlook, and it is inherent in their more or less haphazard and sectional growth that they do not constitute a national health policy. The first essential, in order to avoid overlapping, to secure a full return for expenditure, to keep the services in line with changing circumstances, and to secure that emphasis is distributed according to the social value of the varied services, is to integrate the separate services into a national health policy. The general aim of this policy should be to promote the fitness of the people. The need for such a policy is, among other considerations, reinforced by the fact that the people of Scotland are far short of an attainable standard of fitness, the huge communal

cost of ill-health and the prospect of a declining population. Policy should be comprehensive in scope and should cover the whole field of morbidity.

254. The lines along which health policy should be directed and the adjustments that are necessary in the existing services are discussed in the chapters that follow."

It is to what was said in the chapters concerning the medical services and their administration that I particularly wish to draw attention, comparing the main conclusions and proposals they contain with the system of medical service which is now evolving on the basis of the National Health Service (Scotland) Act of 1947. Let me quote from the Introduction to the part of the Report grouped under the heading "Medical and Allied Services" :—

"459. Evidence on the policy and organisation of the statutory and other services has been submitted to us by Government departments, local authorities (including insurance committees), medical, dental, nursing and other professional organisations, individual doctors and many other interested bodies and persons. The evidence raises many questions of policy and organisation, but *reviewing it as a whole, one major issue, that of the general practitioner in relation to national health policy, stands out for immediate decision.* We find that it enters into our review of most of the services, affecting their work and organisation at many different points, and that a decision on it is fundamental to the problem of their development. We find it necessary, therefore, in presenting the results of our review, to deal with this issue first."

There follows a chapter entitled "Rôle of the Family Doctor." In it the Committee records "the general recognition, by all branches of the profession and by informed public opinion, that the general practitioner, acting normally as family doctor, is an indispensable instrument of national health policy, that without his assistance, as health adviser and as a principal liaison between the homes of the people and the statutory medical services, these services cannot, in modern conditions, function to the full extent as part of a comprehensive policy for promoting and safeguarding the health of the people."

The Committee quotes a number of the statements of evidence which led it to record this "general recognition." The first is from the Consultative Council on Medical and Allied Services of the Scottish Board of Health in a report published in 1920. It has become almost a classic statement of the view it expresses. Here it is :—

"We regard it as of primary importance that the organisation of the health service of the nation should be based upon the family as the normal unit, and on the family doctor as the normal medical attendant and guardian. It is not for disease or diseases in the abstract that provision has to be made ; but for persons liable to or suffering from disease. The first essential for the proper and efficient treatment of individual persons is, therefore, not institutional but personal service, such as can be rendered to the people in their own homes only by a family doctor who has the continuous care of their health ; to whom they will naturally turn for advice and help in all matters

pertaining thereto ; who will afford them such professional services as he can render personally ; and who will make it his duty to see that they obtain full advantage of all the further auxiliary services that may be otherwise provided."

The Cathcart Report goes on :—

"We find that the view expressed by the Consultative Council in 1920 is accepted generally by all branches of the medical profession in Scotland. The evidence of the Scottish Committee of the British Medical Association is largely based on it."

This last statement is not entirely true—even with the qualifying adverb. As a member of the special committee which prepared and presented that evidence I am entitled to say this. While it is true that we fully accepted this admirably phrased expression of opinion by the 1920 Consultative Council we did not, in fact, start from this as a basis but reached it as a stage in an argument founded on something more axiomatic.

It is worth a few moments digression to say something about the B.M.A. Scottish Committee's evidence. When we got down to the job of preparing it we had available to us a number of earlier reports and other documents, including, of course, the Consultative Council's 1920 Report. There was also its English equivalent (commonly known as the Dawson Report) and the Association's own statement of policy on a "General Medical Service for the Nation."

It is interesting to note in passing a rather significant difference between the Scottish and the English Consultative Councils' reports. Characteristically, the Scots endeavoured to get down to first principles, whereas the English, unhappy in the realm of the abstract, soon got down to almost literally concrete considerations. Quite a considerable part of the Dawson Report is taken up with diagrams and plans of various types of hospitals and centres. So far as I know, this report is the author of that chimerical structure, the Health Centre. I think it would be true to say that these two reports set the pattern of subsequent thinking in the two countries on the problems of Medical and Health Service organisation. I shall revert to this point later.

With varying emphasis all the reports we studied stressed the importance of the general practitioner in any medical service, though it is perhaps worth noting that the Dawson Report nowhere refers to him as the "family doctor." In none of them, however, was any attempt made to explain *why* this view was taken or how it was reached. Our Evidence Committee felt that this was to fall into the common error of the expert who expects his *obiter dicta* to be accepted without question. Though we fully accepted the view, we thought it desirable that supporting evidence should be adduced in order to convince a body which would—quite rightly—be critical of anything we had to say. In doing this we were helped by the dawning appreciation of

what has now come to be known as Social Medicine, and in our evidence we stated that :—

"Recently a reorientation of medical thought has occurred and the basis has been widened. In the modern, wider concept, medicine has come to be regarded as applied human biology. From this point of view the state of health of an individual at any time is the measure of his success in reacting to his environment. It is our opinion that many of the present-day health measures are misdirected, for the very reason that they are based on what for convenience may be called 'the pathological conception of disease'."

From this we developed the theme that if health is a matter of the reaction of an individual to his environment, it follows that the person who is to give him expert advice on health should be one who, to the greatest possible extent, is familiar both with him and his environment, and that such a one is to be found in the person of the family doctor.

Other bodies, such as the Royal College of Physicians and the Royal College of Surgeons of Edinburgh, unequivocally proclaimed the same faith, the former describing the family doctor as "the pivot of all schemes which concern the national health," and the latter family practice as "the basis of the health services rendered to the community by the medical profession." Even Medical Officers of Health—not always regarded as the most enthusiastic of supporters of the general practitioner—were numbered among the host. "From the health point of view," said one of them, "I am satisfied that the family must be the unit and that the family health must be looked after by the general medical practitioner." I am bound to say that, as a loyal M.O.H., he added at the end, "in association with the health visitor."

In the face of such remarkable agreement it is not surprising that the Cathcart Committee accepted this point of view, and adopted it as the central theme of the Report. (By a curious chance the pages dealing with it are the central pages of the Report!) The theme is even carried into the realm of prognosis. In one of the sentences in a short General Conclusion the Committee says :—

"In modern conditions, we think, the State must depend increasingly on the general medical practitioner, acting normally as family doctor, for the medical contribution to further progress in public health"

Let me now recall briefly how the Cathcart Committee considered that this primary requirement should be provided. In this connection the following quotations are interesting :—

(1) "The only expressions of opinion in evidence to us in favour of a whole-time general medical service were those of the Corporation of Glasgow, of the Scottish Trades Union Congress General Council and of one medical man."

(2) "All the medical organisations expressed themselves strongly against a whole-time salaried service. The main reason put forward was the importance of retaining in medical practice free choice of doctor, as an essential condition of confidence between doctor and patient, and the impracticability of providing for free choice in a whole-time medical service."

The Committee fully considered and fully discussed in the Report the pros and cons of a whole-time salaried service of general practitioners, but came down on the side of the doctors. Here is its conclusion on this controversial topic :—

“ This co-ordinated service should be based, as far as possible, on the family doctor, who should act as health adviser and in liaison between the homes of the people and the statutory health services. The basis of employment of the general practitioner should be, as in the national health insurance scheme at present, by contract for part-time services remunerated by capitation fees. The principle of free choice of doctor, as in the national health insurance scheme, should be preserved.”

It may be remarked that I have made no mention of what the Report has to say of the hospital and specialist, the public health and other services which go to make up the total of effort our community has made to deal with its sick and maimed. These are, of course, all dealt with in this wide and comprehensive survey. But it would be impossible in the time available to summarise accurately all that is said in a report which is comparable in length with a Walter Scott novel and is itself no mean feat of compression and condensation. Nor is it desirable or necessary for my purpose to do so. What I am concerned to do is to show that at that time—some fifteen years ago—there was a remarkable consensus of opinion amongst the profession in Scotland as to what was the primary requirement of efficient medical provision for the people of Scotland and that the Profession was able to persuade a predominantly lay committee to accept its view ; and, further, that there was a wide measure of agreement among all concerned as to how this primary requirement should be provided.

If I have perhaps seemed to labour the point, I must say in defence that I was anxious to avoid being classed with the advocate who finished his peroration to the jury with the sentence, “ These, Gentlemen, are the opinions on which I base my facts.”

The question now arises, have these opinions and agreements changed ? For my part, I believe not. Certainly they have been befogged and bedevilled by the irrelevancies of doctrinaire politics, which so unfortunately it has proved impossible to avoid in the necessary process of legislation. But the Scot is canny and his mind is logical. He neither reaches nor changes his opinion quickly or without good reason. By and large, too, he keeps his thalamus under better cortical control than does the inhabitant of more southerly parts of our island.

I must now, in order to complete my picture, sketch in something of the administrative ideas of that time. The B.M.A. Scottish Committee, reasoning from its conception of a basic family doctor service extended to include appropriate economic groups and expanded by the provision of the hospital, specialist and other necessary services, argued that, since you must draw your administrative line somewhere,

the proper place to draw it was round the essentially medical services as distinct from "health" services, such as sanitation and housing. It further argued that geographical, transport and similar factors had already resulted in a natural regional development and that this fact should be taken into account in determining the appropriate area of administration. These regions did not correspond with any existing local government areas and for this and other reasons it advocated *ad hoc* regional medical boards, dealing with regions large enough to provide all the ordinary medical services. This proposal would have involved the abolition of the National Health Insurance Committees and the removal from local authorities of all medical administrative functions. I still think that this is the most practical and sensible approach to the administrative problem and that we shall come to something like it in the end.

The Cathcart Committee, though it recommended the abolition of the Insurance Committees and the transfer of their functions to the appropriate local authority, could not bring itself to support the Association's more radical proposal except in relation to a possible complete overhaul of the machinery of local government. It did, however, accept the principle of a common administrative body for all *medical* services as the following quotation shows:—

"To equip the local health authorities to deal comprehensively with the health problems of their areas, it is *essential*, we think, to bring the general practitioner and other medical services under one administration."

If, then, the view in Scotland has remained substantially constant, what of the National Health Service Act and the service we are trying to build on it? Are they the kind of thing the Cathcart Committee had in mind? A practically unqualified "No" is the only answer one could possibly give to this question. It is inconceivable that, had the legislation been based on the Cathcart Committee Report, anything like the present Act would have resulted. One has only to consider the Parts of that Act and their order to realise that its origin was something quite different. The Act does not begin by prescribing the necessary statutory arrangements for the basic and primary service, but with those relating to the transfer to the State of the ownership of the hospitals—a step, incidentally, which was deliberately rejected by the Cathcart Committee. The provisions for general practice do not even come next, but third, and after those for what remains to local authorities of their health services.

The order of setting out the provisions of an enactment is no doubt not a matter of great practical importance, but it must be significant to some extent of what is in the minds of the legislators. The *content* of Part IV—the general services—is more important. Insurance Committees were, as they had to be, abolished, but were replaced by bodies, which, though improved in constitution, are essentially similar and quite divorced from the administration of either the hospital or



the local authority services. One small concession is made to the conception of a co-ordinated service which the Cathcart Committee pressed so strongly. In the Scottish Act—but not in the English—is a small section (Section 30) permitting but not requiring local authorities to expend money on the setting up of liaison committees in their areas representative of the three administrative bodies under the Act. Attempts to implement this provision have so far met with very limited success and it seems doubtful if much is to be expected from it.

I said earlier that I should revert to the point that the two Consultative Council Reports of 1920 had set the pattern of administrative medical thinking in the two countries. Here, I think, lies the explanation of the form of our Act. Rightly or wrongly it seems to be considered necessary with our present legislative machinery that a Scottish Act of Parliament must so closely resemble its English counterpart as to be distinguishable only by the faint Caledonian flavour of its language. Be that as it may, there is little doubt in my mind that it was principally conceived in the minds of Whitehall. The basic ideas came to these minds from the Dawson Report and the whole is, of course, strongly tinged with the cochineal of Transport House and its medical pundits. I think I can detect—and this is rather curious—a definite flavour of Harley Street. Indeed, in bitter moments, I have wondered if N.H.S. stood for Nationalised Harley Street!

Let me mention just two of the results of the first year's operation of the Act. The accounts of the Executive Councils for this year are now available. From them we learn that in Scotland the average net income of dentists was £1780 and of general practitioners £1130. Leaving aside the rightness or wrongness of these incomes and without any wish to disparage the work of a sister profession, one can scarcely conceive anything further from the ideas of the Cathcart Committee than a scheme which rewards the family practitioner at a rate of about two-thirds of the dentist. It is not necessary to point out to this audience that, since this is the *average* figure, the majority of practitioners are making net incomes of less than £1100, and that many of these are capable and experienced men. It is one of the more distressing results of the introduction of this service that many of our best and most conscientious practitioners are suffering severe financial hardship just because they have built up the kind of family practice which we would like to see available for all.

In many of our small towns the inhabitants, with the enthusiastic support of their doctors, have built and equipped small hospitals with mutual benefit to all concerned. Now, in at least one region, some of these hospitals have been closed to the general practitioners who have staffed them for years. The consequence of this ridiculous step is particularly obvious in relation to midwifery. Now, a woman who for several good reasons, including the distance of her home from her doctor, wishes to have her baby in hospital but would like to be looked after by her own doctor cannot do so. One can scarcely imagine

anything more calculated to depress the standard of general practice and discourage recruitment to its ranks than the deliberate exclusion of the practitioner from the hospital. It is a policy which should be completely reversed.

Now supposing I am right in believing that the Act largely ignores Cathcart, does this matter greatly? Does it mean that it is impossible on it as a basis to build up in the course of the years the kind of scheme the Cathcart Committee had in mind? I believe we can confidently answer "No, if . . ." But the "if" is very important and it is chiefly concerned with us as the doctors of Scotland.

There is abroad among us to-day an almost universal sense of frustration. There is also a tiredness, which is perhaps in part the result of this frustration and reciprocally increases it. There is, I believe a real danger that, unless we summon to our aid the independence and tenacity of purpose so signally the attributes of our forbears, this state may lapse into shoulder-shrugging apathy and a peevish "what's the use?"

The Act is essentially an enabling Act and depends for its effect on the Orders and Regulations promulgated under it. As a profession in Scotland we have been and will be consulted about these. Neither the Act nor its Regulations is sacrosanct. They can and obviously must be amended.

It will be neither an easy nor a short job. But in our Association we have the means to fashion the tools we shall need. If each and every one of us will give of his best in wisdom and patience in the using of them, I have no slightest doubt that we shall succeed. There is but one further point I should like to make before I finish. In a most interesting Saltire Society pamphlet on *The Scottish Legal Tradition*, Lord President Cooper says, "No one imagines that there exists amongst English lawyers any conscious desire to interfere with Scots Law; for the first Article of the English lawyer's creed is that English Law is so incomparably superior to other systems that the others are hardly worth a glance, and there are few subjects on which England is so contentedly ignorant as Scotland and her institutions. The truth is that law is the reflection of the spirit of a people, and so long as the Scots are conscious that they are a people, they must preserve their law." I suggest that the way in which it provides for the care of its sick is also a "reflection of the spirit of a people," and that what is true of Law is also true of Medicine.

In *Scottish Medicine* we inherit a tradition of contribution and service second to none. I have tried to show this evening that much of that tradition is translated into the practical terms of a programme in a report which is available for our guidance. If we would be worthy of our inheritance we can scarcely do better than take as our blue-print what I have described as the Forgotten Report.

## NOTE

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh. The following passed the Final Examinations, and were granted the diploma of

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## NEW BOOKS

*Selected Writings of William Clowes, 1540-1604.* Edited by F. N. L. PAYNTER, B.A. Pp. 179. London : Harvey & Blythe. 1948. Price 15s. net.

Clowes was a prominent surgeon of the days of Queen Elizabeth, well-trained, observant and open-minded. He wrote three books, one on syphilis, one on struma and one on surgery, and in order that they might be helpful to poorly educated apprentices he wrote in English. The editor provides a biographical account of Clowes' life and he has made a happy selection from his works. For the most part these are histories of surgical cases but they contain much interesting information about other practitioners, physicians and quacks. This book gives a good idea of medical practice of the times and is both instructive and entertaining.

*Atlas of Human Anatomy.* Vol. I. By M. W. WOERDEMAN, M.D., F.R.N.A.S.C. Pp. 440 and index, 665 illustrations. London : H. K. Lewis & Co. Ltd. Amsterdam : Wetenschappelijke Uitgeverij. 1948. Price £3, 10s. net.

This atlas is intended primarily for medical students. Vol. I deals with bones, joints and muscles ; Vol. II will include the remaining systems, except that peripheral vessels and nerves will be in Vol. III along with X-rays and Regional Anatomy. What might be termed a visual description of each structure is given by means of separate drawings followed by regional drawings of dissections. For example, individual muscles are placed diagrammatically on drawings of the skeleton, to show attachments and action, and are repeated with their neighbours in drawings of appropriate dissections. The preface and a few explanatory notes are in English ; the Basle Nomenclature is used for labelling the illustrations. The statement that " All details, including those visible only by means of a lens, have been accurately reproduced in the plates," may explain the lack of crispness in some of the drawings. They improve on acquaintance, however, and students using the atlas properly will benefit greatly.

*The Parathyroid Glands and Metabolic Bone Disease.* By FULLER ALBRIGHT, A.B., M.D., and EDWARD C. REIFENSTEIN, Jr., A.B., M.D., F.A.C.P. Pp. xxvi+393, with 157 figures. London: Baillière, Tindall & Cox. 1948. Price 44s. net.

This is an important book which will be of value not only to the endocrinologist but also to the general physician. One of the authors has already established a world reputation for his work on parathyroid disorders and most of us are familiar with his views. We are presented here with a summary of his studies on calcium metabolism carried out at Massachusetts General Hospital over the past twenty-four years. The way in which the authors marshal their facts and the closely reasoned arguments which support their conclusions are a model of scientific method. The photographs and diagrams with which the book is plentifully illustrated are of a high standard, in keeping with the text, and greatly enhance its value. Any possible criticism is forestalled in the preface, which is in itself a critical review.

*Brief Psychotherapy: A Handbook for Physicians on the Clinical Aspects of Neuroses.* By BERTRAND S. FROHMAN, M.D. Pp. 265. London: Henry Kimpton. 1948. Price 20s. net.

The author has had ten years' experience in general practice and fifteen in clinical psychotherapy. He intends the book for physicians generally and not for psychiatrists. He is an eclectic psychotherapist, refers to Freud a good deal and appears to have been a pupil of Stekel. A brief but succinct account of Korzybski's general semantics, used as an adjunct to psychotherapy, is included.

The book deals almost entirely with the neuroses and is of uneven quality and the presentation is rather fragmentary. Nevertheless, it is clear, and makes many telling points. One hundred cases are reported, usually each consisting of one paragraph illustrating one single point. Frohman favours brief and active psychotherapy and his illustrations thereof are one of the best parts of the book.

*Collected Papers of the Mayo Clinic and the Mayo Foundation.* Vol. XXXIX. Edited by R. M. HEWITT, M.A., M.D., and others. Pp. x+871, illustrated. London: W. B. Saunders Company. 1948. Price 63s.

The Mayo Clinic volume takes a well-deserved place in medical literature. This issue contains the papers of the year 1947, well over 200 of them, arranged in sections representing various specialties of medicine and surgery. There is a great wealth of material giving the latest views in many fields of activity. Many of the articles have been reprinted from *Journals* not ordinarily accessible in this country and in addition papers published by the Staff in "Medical Clinics," "Surgical Clinics" and "Proceedings of the Staff Meetings" are given by title. The book is a useful guide to recent progress.

*The Surgery of Abdominal Hernia.* By GEORGE B. MAIR. Pp. 408, with 138 illustrations. London: Edward Arnold & Co. 1948. Price 25s. net.

That recurrence follows one in every four or five operations for inguinal hernia is sufficient justification for the publication of this stimulating and exhaustive monograph in which inguinal hernia rightly receives lengthy and detailed consideration. Most surgeons will disagree with something in this book but none can read it without advantage. The author condemns the Bassini operation and advocates herniotomy with the addition, under certain carefully defined conditions, of a fascial suture. In advocating the use of grafts of whole skin instead of fascia, the author gives a good description of the method and of the precautions essential to success. The only notable omission seems to be that of the observation of the effect of a sudden increase in the quantity of oxygen inspired by the patient when judging the viability of bowel from a strangulated hernia; this valuable test deserves wider knowledge and might be included in subsequent editions.

## NEW EDITIONS

*Cunningham's Manual of Practical Anatomy.* Vol. III. Edited by J. C. BRASH, M.C., M.A., M.D., F.R.C.S.E. Eleventh Edition. Pp. x+513, with 213 figures and 16 plates. London: Oxford University Press. 1948. Price 21s. net.

This volume deals with the head and neck and includes the ear, eye and brain. The principal change in this volume is in the suggestions for dissection of the brain where the most logical approach from the hind-brain upwards is now recommended. Careful revision has been carried out, old illustrations have been replaced and new ones added. The manual is a first-class production which should maintain the reputation of previous editions of this work.

*Diabetic Manual.* By ELLIOTT P. JOSLIN, M.D., SC.D. Eighth Edition. Pp. 260, illustrated. London: Henry Kimpton. 1948. Price 12s. 6d. net.

This book, written for both the patient and his doctor, has already had a long and successful run. It contains a thoroughly good and clear account of diabetes and how it may be controlled, and also of the possible dangers, their prevention and treatment. Full details of dietary management and of the use of insulin are given and the matter has been presented in such a way that any layman may understand. A most useful and valuable book.

*Cunningham's Manual of Practical Anatomy.* Vol. I. Edited by J. C. BRASH, M.C., M.A., M.D., F.R.C.S.E. Eleventh Edition. Pp. xix+387, with 191 illustrations and 44 plates. London: Oxford University Press. 1948. Price 21s. net.

Dr E. B. Jamieson having retired after long service to anatomy, has been succeeded by his co-editor, Professor Brash. The latter has undertaken a complete revision of this well-known work while still retaining the general arrangement that has stood the test of time for so long. New material in Vol. I includes a series of X-rays showing the epiphyses and also some others which show the course and anastomoses of injected arteries. This guide to dissection should continue to serve further generations of students.

*Clinical Roentgenology of the Digestive Tract.* By MAURICE FELDMAN, M.D. Third Edition. Pp. ix+901, with 641 illustrations. 1948. London: Baillière, Tindall & Cox. 1948. Price 44s. net.

This is a volume of outstanding merit for not only is it informative and accurate but it is eminently readable and interesting. Written with authority expressive of experience but without being over-dogmatic, it is always thought provoking and stimulating. It will appeal both to the clinician and to the radiologist and serves usefully to place in proper perspective their different fields. The illustrations are well chosen, adequately described and beautifully produced; they are always easy to follow, for the salient features are clearly indicated by arrows or other suitable indices, and numerous lucid diagrams have been added. The text is full of clinical material and is so arranged that the salient facts can be easily picked out.

*Psychiatric Examination Card: Extended History in Cases of Neurosis.* By A. SPENCER PATERSON. Second Edition. Size 5½" by 4½". London: H. K. Lewis & Co. Ltd. 1948. Price 9d. net.

This is a single pocket-size card, supplied in a transparent envelope. Each side gives the main headings and a number of specific questions to be asked in a first, or diagnostic, interview with (1) psychotic patients and (2) psychoneurotic patients.

*Clinical Methods in Surgery.* By K. DAS, M.B., F.R.C.S. Second Edition. Pp. viii+255, with 249 illustrations. Calcutta: The City Book Company. 1948. Price 35s. net.

This book has proved popular and a new edition has been called for within a year of its initial publication. It is written for the student who is starting clinical surgery. The first chapter describes the general plan of taking a case history. Thereafter the examination of the various systems is dealt with more fully. The undergraduate is told and often shown by diagram how to investigate a case, what things to do, how to carry them out, and in what order. Although the colour plates are disappointing, the other illustrations are both numerous and good. The best feature of the book is its teaching that there must be a definite system and order in all clinical examinations.

*Groves and Brickdale's Textbook for Nurses.* Edited by J. A. NIXON and Sir CECIL WAKELY. Seventh Edition. Pp. 689, with 248 illustrations. London: Oxford University Press. 1948. Price 30s.

In this revised edition of a well-known book, the diet and vitamin charts have been modernised; the section on physiology of nervous system has received some welcome pruning; an excellent chapter on virus and infection has been added; and the part dealing with medical tuberculosis has been entirely rewritten. The signs, symptoms and course of disease are clearly and accurately explained, but too often modern ideas in treatment have been dove-tailed into older methods and this results in some surprising omissions and inclusions.

*Plaster of Paris Technic.* By EDWIN O. GECKELER, M.D. Second Edition. Pp. xiv+220, with 236 illustrations. London: Baillière, Tindall & Cox. 1948. Price 16s. 6d. net.

Calot, in his book on *Orthopædic Surgery*, said "Show me your plaster and I will tell you what sort of orthopædist you are." In this handbook an attempt is made to teach the beginner the correct application of the immobilising plaster case. The first few chapters are devoted to the forms of plaster of paris used in surgery, the technique and application, and to the errors and difficulties. Thereafter the application to each region of the body is described.

Orthopædic technique and the reduction of fractures have been intentionally avoided but full instructions are given for the application of the plaster. The book is well written, fully descriptive, and copiously illustrated, and will be of great value to the young orthopædic surgeon.

*Symptoms in Diagnosis.* By J. C. MEAKINS, C.B.E., M.D., D.S.C., LL.D. Second Edition. Pp. xv+542, with 112 illustrations. London: Baillière, Tindall & Cox. 1948. Price 42s. net.

It is well established that the patient's symptoms are of far greater importance in the diagnosis of disease than physical signs or laboratory investigations. The symptomatology of disease is the most subtle of all diagnostic criteria and it is therefore essential to sift all the evidence presented by the patient before one is able to reach a final and correct diagnosis. The author has discussed and carefully analysed the many and varied symptoms of disease processes and has given his conclusions of nearly forty years of experience of such symptoms in clinical medicine.

The second edition of this book has been brought up to date with the clinical advances in medicine. The symptoms of disease are carefully classified into systems and are discussed at length in the light of their importance in diagnosis. This book should be of great value to every practising physician.

*Recent Advances in Cardiology.* By T. EAST, M.A., D.M., F.R.C.P., and C. PRAIN, M.C., D.M., F.R.C.P. Fourth Edition. Pp. x+454 with 98 figures. London: J. & A. Churchill. 1948. Price 24s.

The third edition of this work appeared in 1936 and the great increase in knowledge since that time has justified a complete re-writing of the text. The whole field of cardiology has been reviewed and so completely that the book presents a fairly comprehensive account of cardiovascular diseases. In their task the authors have kept in mind the needs of the modern practitioner as well as the student working for a higher qualification and to both of these classes we can thoroughly recommend the new edition.

*The Diabetic A.B.C.* By R. D. LAWRENCE, M.A., M.D., F.R.C.P. Tenth Edition. Pp. vii+80. London: H. K. Lewis. 1948. Price 4s. net.

The steady flow of fresh editions gives a good idea of the continued popularity of this little book. Written primarily for nurses and patients it contains a good deal of information of the greatest value to the practitioner. Special attention has been given to post-war difficulties in dieting. Otherwise there are no fundamental changes.

## BOOKS RECEIVED

- BIGGER, JOSEPH W., M.D., SC.D. (DUBLIN), F.R.C.P., F.R.C.P.I., D.P.H., M.R.I.A.  
*Handbook of Bacteriology.* Sixth Edition. (Baillière, Tindall & Cox, London) 20s. net.
- BROCKBANK, E. M., M.B.E., M.D. (VICT.), F.R.C.P. The Conduct of Life Assurance Examinations. Third Edition. (H. K. Lewis & Co. Ltd., London) 12s. 6d. net.
- CLEMENTS, F. W., M.D., D.P.H., D.T.M. Infant Nutrition: Its Physiological Basis. (John Wright & Sons Ltd., Bristol) 21s.
- CROWE, H. WARREN, D.M. (OXON.), B.CH., M.R.C.S., L.R.C.P. Rheumatism. Second Edition. (Staples Press Ltd., Lonaon) 17s. 6d. net.
- Editors: JONES, HAROLD WELLINGTON, M.D., HOERR, NORMAND L., M.D., and OSOL, ARTHUR, PH.D. Blakiston's New Gould Medical Dictionary. (H. K. Lewis & Co. Ltd., London) 45s. net.  
 Thin Paper Edition 55s. net.
- Edited by WEBER, F. PARKES. Further Rare Diseases and Debatable Subjects. (Staples Press Ltd., London) 25s. net.
- FRANKLIN, KENNETH J., D.M., F.R.C.P. A Short History of Physiology. Second Edition. (Staples Press Ltd., London) 10s. 6d. net.
- GUTHRIE, DOUGLAS. Lord Lister: His Life and Doctrine. (E. & S. Livingstone Ltd., Edinburgh) 15s. net.
- LEITCH, ALFRED, M.B., CH.B. (EDIN.). The Tuberculous Process. (John Wright & Sons Ltd., Bristol) 12s. 6d.
- MACDONALD, DAVID MITCHELL, M.D., D.P.H., F.R.C.P.E. Revised by CRUIKSHANK, ALISTAIR G., F.R.C.P.E. The Pocket Prescriber and Guide to Prescription Writing. Fourteenth Edition. (E. & S. Livingstone Ltd., Edinburgh) 4s. 6d. net.
- MCDUGALL, JOHN B., C.B.E., M.D., F.R.C.P. (EDIN.), F.R.F.P.S. (GLAS.), F.R.S.E. Tuberculosis. (E. & S. Livingstone Ltd., Edinburgh) 32s. 6d. net.
- MARQUARDT, MARTHA. Paul Ehrlich. (William Heinemann (Medical Books) Ltd., London) 25s. net.
- SIRI, WILLIAM E. Isotopic Tracers and Nuclear Radiations with Applications to Biology and Medicine. (McGraw-Hill Publishing Co. Ltd., London) 106s. 6d.
- SPELLER, S. R., LL.B. of Lincoln's Inn, Barrister-at-Law. Law Relating to Hospitals and Kindred Institutions. Second Edition. (H. K. Lewis & Co. Ltd., London) 44s. net.
- WESTON, H. C., F.I.E.S. Sight Light and Efficiency. (H. K. Lewis & Co. Ltd., London) 42s. net.
- The Proceedings of the Ninth International Congress on Industrial Medicine. London, 13th-17th September 1948 (John Wright & Sons Ltd., Bristol) 60s.

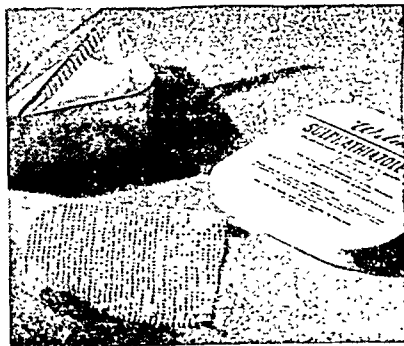
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# Edinburgh Medical Journal

November 1949

## FREEDOM OF THOUGHT IN SCIENCE

By FREDERIC WOOD JONES, D.Sc., F.R.S., F.R.C.S.

Sir William Collins Professor of Human and Comparative Anatomy in the  
Royal College of Surgeons of England

WITH the passage of time there comes to most of us a realisation of the hollow vanity of the boasts that were so confidently enshrined in some of the slogans current in our youth. More recent experiences have shaken my belief in the oft-repeated assertions that the inhabitants of the British Islands enjoy such a degree of democratic freedom that under no circumstances could they ever become slaves. I no longer believe that the sanctity of my home is so assured that it may be regarded as being as completely inviolate as if it were my castle. None of us who has followed recent trends of events can still continue to have any delusion as to the freedom of expression of opinion, or even of the freedom of thought itself. Freedom of speech has for long been rightly claimed as an essential of human social organisation. Freedom of thought, even when unexpressed overtly in speech or action, has, of ancient tradition, been respected as being the inviolate right of the individual thinker. When freedom of thought is denied to the individual by authority, we may be assured that human social organisation has almost reached its lowest depths.

It may, however, be urged in such a company as this that, although in the uneasy realm of politics these things may be true, fortunately, in the sphere of scientific research there is still an absolute freedom of action, of expression and of thought, permitted to the worker engaged in the great search after truth. Possibly such a state of things did exist in most scientific fields in times not so very far distant: but to-day we must all admit that, if the quest of the scientific worker may by chance lead to any improvement in the methods of wholesale human slaughter, the scientist has ceased to be able to act, to speak, or even to think as a free man. Any scientific man whose special line of investigation may involve, even remotely, the question of the wholesale destruction of his fellows is, unless he possesses a strength of character not commonly met with in these days, a slave to whom the freedom of expression or even of thought itself is absolutely denied. This we all know to be true. There is no need to quote references to the published accounts of recent happenings which should make us all aware of the fact that there is no such thing as freedom of thought, of expression of thought or of direction of enquiry in any branch of physical science that may

possibly impinge upon the methods of mass destruction of humanity, or the politically engineered promotion of war between peoples to whom the very idea of warfare is wholly repugnant.

This regrettable state of affairs naturally prevails almost exclusively in the realm of the physical sciences, but already we are becoming familiar with the term "biological warfare" and it seems possible that, even in the sphere of the study of life, the future may see imposed all those measures of secrecy, of restriction of expression and the direction of enquiry that at present are so stultifying in certain branches of physical research. But save in the case of those scientific researches that might possibly have some bearing upon warfare, it would generally be accepted that biological science is free from tyranny imposed by authority. It may be at times dominated by theories and fashions of thought, but it is commonly conceded that every man is free to hold and so express his own opinion. Nevertheless, although that is true enough as a general concept, it is possible that freedom of scientific thought in biological science is not so absolute as many sincerely believe it to be.

At the present time, the very subjects that we are about to discuss are enmeshed in a strangling dodder growth of political doctrines to such an extent that their dispassionate discussion has become, to those for whom political doctrines override scientific detachment, an almost impossible task.

In the story of the acquirement of knowledge in any branch of science, there is always a sequence of changing theories and the alternation of opinion as to orthodoxy and heterodoxy. This is merely the expression of that natural ebb and flow of thought that must ever accompany the progress of knowledge; and in the case of most biological subjects it means no more than that. It is only when scientific orthodoxy becomes synonymous with political orthodoxy that danger to freedom of thought is a real threat.

But there is a factor far more important than the ordinary profit and loss account of current opinion in determining what is to be accepted as scientifically orthodox and what rejected as heterodox. This all-important factor is the limitation of language, and so of thought, to a definite trend of mental bias to which all men are heirs. This being the case, it must of necessity come about that all scientific theories are liable to suffer from an inherent bias and, therefore, that which is held to be orthodox will always be the view that seems most reasonable and natural to those minds the thought processes of which are warped always in one direction. We may probably rightly claim that in pure academic science there is no sort of limitation of the freedom of thought and expression: but we must never forget that there is an inherent bias in all human thinking. There may be, theoretically, perfect freedom of thought in scientific circles; nevertheless, I fancy that to-day it would be very indiscreet for any young man, having any regard for his career in science, to occupy the time of a learned society in an attempt to persuade its members to a belief in the doctrines of

vitalism, teleology or Lamarckism. Here, and as a tribute to Struthers, the master anatomist, we are undertaking the unpopular task of claiming that this trinity of beliefs is the only true teaching that lies at the base of all biological science.

The doctrine of vitalism we will define as a thesis that claims for the living organism a fundamental distinction in behaviour from that displayed by non-living matter. As for the nature of this distinctive feature of life, there is no better statement than that of E. S. Russell, who has declared that "biology must recognise and accept directive activity as an 'irreducible characteristic' of life." No such quality as directiveness is to be detected in the non-living. Adherence to such a belief in the directive activity of life naturally entails an advocacy for the doctrine of teleology, for if directive activity is the characteristic of the living organism, then we must recognise "that developments are due to the purpose or design that will be fulfilled by them" (*O.E.D.*). At this point the vitalist, who is prepared to become a teleologist, must pause on the verge of acknowledging the inherent probability that developments, due to the purpose that they will fulfil, will be likely to become incorporated in the hereditary make-up of the animal. Should he be prepared to take this further step, he must face the fact that he has now embraced the whole trinity of scientifically infamous doctrines—he has become a believer in the inheritance of so-called acquired characters and has joined the ranks of the despised Lamarckians. It is these doctrines that the young man at the outset of his career should refrain from defending; for he must not forget that however well founded his opinions may be, he labours under the disadvantage of having no proper language in which to think of, or with which to express, vitalistic happenings. He must remember that we are all the slaves of mechanistic imagery, and dependent on a mechanistic vocabulary, and, for that very reason, vitalistic theories will always be unorthodox, when orthodoxy is assessed by aptitude in verbalism. It is, I think, beyond denial that verbalism reigns supreme in science to-day. The exponents of the biological sciences, bereft of proper language in which to think and in which to express their thoughts, are engaged in coining a pseudo-biological jargon intended to conceal the basic poverty of the underlying thought processes. The reader of the modern literature of, say, psychology or genetics, must be bewildered by the verbal smoke screen that envelops the discussion of even the most commonplace manifestations of mental, or reproductive, activity and so produces an entirely false atmosphere of assurance as to the profundity of our knowledge concerning them.

#### VITALISM

There are many who feel that the great Linnæus was not at his happiest in selecting *sapiens* as the specific name for *Homo*. Perhaps a more fitting designation would have been *Homo faber*, for man is distinguished among animals by the fact that he is the tool user. With the first hurling of stocks and stones as missiles and the first fashioning

of a stone implement with which to scrape, or cut, or pound some other object, man became what he has always remained—a thinker in terms of physical forces and physical properties. When, later in the story of human progress, man began to understand and to apply physical forces and so to invent simple mechanical contrivances, his mental processes were already coloured by mechanistic imagery and, with each new mechanical triumph, this imagery became more complete and more dominant. Long before any of the great problems of life and living had appealed to him as being worthy of his attention he had become accustomed to think in terms of physical forces and mechanistic principles. Function, as manifested by living things, could only be likened to the working of the mechanical contrivances that man had devised. Language and thought are so interwoven that the two constitute a unit. The age-old mental bias towards mechanistic imagery begot and standardised a vocabulary founded wholly upon physical conceptions. Biologists—the students of life—must always be under the handicap of studying a subject the findings of which they are unable to formulate, or to discuss adequately, by reason of the fact that they can only do so in the highly inappropriate language of the mechanist. It is unfortunate that biologists do not always appreciate this basal fact. It is also unfortunate that sometimes they forget that, though they are forced to think and to speak of vital phenomena in terms of pure physical mechanism, they may not rightly urge this unfortunate handicap as evidence that vital phenomena are no more than simple mechanisms. It would be better for science were it to be generally acknowledged that, though the physical sciences have an ample and ever-increasing vocabulary with which to express their findings, the biological sciences possess no language of their own. Should we wish to define our most intimate emotions, or lay bare our most elusive psychic processes, it is in terms derived from, and appropriate only to, physical phenomena that we must allude to them. As a consequence of some psychic upset an individual may manifest the emotional phenomenon of rage. How can we express the phases or the life history of this psychic vital phenomenon, even when it is manifested in our own psychic experience? Rage may simmer, seethe, smoulder, fume, boil or burn. It may flare up, blaze forth, flash out, cool down or pass to the white heat of passion. It can do all these physical things and many more; but it can do nothing that cannot be described solely in terms derived from and appropriate only to physical happenings. It is the same with every vital phenomenon. All living function must needs be thought of and expressed in terms of mechanical contrivances. Every little mechanical and physical invention that man has achieved has been pressed into the service. Levers and pulleys, pumps, furnaces, bellows and engines of all sorts have been drawn upon for similies and for terminology and these have, from sheer necessity, been employed by the biologist in his thinking and in his imagery of vital phenomena. The machine has exercised its tyranny in the realm of human thought. Electricity has been seized upon by

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neurologists as a drowning man clutches at a straw and a mechanistic jargon passes current as a substitute for knowledge. Surely, if these limitations imposed by an unavoidable bias towards mechanistic imagery were realised by orthodox biological science, more tolerance would be extended to those who believe that the living organism is something not, in all its activities, necessarily subject to the so-called laws that apply to lifeless matter. In 1913, Lawrence Henderson wrote "Vitalism has perhaps not had a positive success in three centuries. Such a history no doubt depends upon the inherent and inevitable weakness, within the domain of science, of vitalistic views." It is possible that this lack of success is due, not so much to an inherent weakness in the thesis, as to an inherent weakness in our methods of thought and expression. It may be true that, in the discharge of its functions, the living organism conforms to most of the recognised chemical and physical principles applying to the non-living; but it is a mistake to suppose that because of this the living organism is no more than a physico-chemical mechanism.

As Russell has said in regard to Sherrington's claim that in the marvellous laboratory of the cell "each and every step is understandable chemistry," "Surely the difference between an inorganic and an organic system lies not in the greater complexity of the latter, but in the orderly directiveness of its activities towards the ends of living, developing and reproducing? If we treat them both as energy systems differing merely in complexity, we leave out what is distinctive of the organic system. But why disregard the vast differences between the living and the non-living, the directiveness, orderliness, adaptability and creativeness of organic activities, which are so patent and obvious characteristics of living systems, and lacking in the inorganic world?"

The precise relation of living to non-living matter is at present beyond the reach of the human mind, but curious vistas may even now be opened up in which everyone is free to indulge in day-dreams. It is even possible to speculate if inanimate matter, with which we are so familiar in the composition of our earth, has always been as lifeless as it is to-day. It may be that life has had more to do with the making of inanimate matter than is generally supposed. For the vitalist, there is satisfaction in the knowledge that the vast rolling downs of chalk, the hidden wealth of the coal measures, the limestones and so many other geological formations are demonstrably the products of life. In the ordinary common sense contemplation of our home in the universe, it would seem that the living organism has taken a very dominant part in providing the lifeless bricks and mortar of which our home is built. In last resort, the vitalist may remind the mechanist that though the chemistry, the physics and all the other attributes of chalk and flint and coal are familiar enough, there is behind them all the vital activity of the living organisms that made them in the distant past. Like the cheese mites that argued learnedly as to the origin of the cheese in which they lived, the mechanist is in danger of overlooking the presence of the cow in the background of the building of his home in the universe.



Reviewing the recent trends in the development of biological thought, it may be claimed that there is no reason whatever why those who believe that living organism is something distinct from inorganic, lifeless matter, should shrink from defending this thesis. It is the prejudice begot by our age-long habit of mechanistic thinking, and not real scientific knowledge, that dictates a disbelief in the uniqueness of the processes that constitute the phenomena of life.

### TELEOLOGY

The living organism is for ever in a state of flux. Life is always undergoing phases of ebb and flow and the arrest of this process of dynamic instability results of necessity in a cessation of life. The perpetual fluctuation of composition and of form that typifies living matter in its simplest manifestation is merely an expression of the fact that every living organism is a complex of function and structure. Function and structure constitute the indivisible unit that is the essence of life ; and both partners are forever in a state of being, of emergence and of passage. Their interdependence is constant ; their state is one of perpetual transition. It is, as John Hunter recognised two centuries ago, a vain quest to attempt to solve any of the problems connected with living organisms by studying only one of the twin factors that constitute the basis of life. Life must be studied as a whole if we are to attempt its understanding.

It is a regrettable fact that the study of the living organism has, with the specialisation consequent upon the vast accumulation of unrelated facts amassed during the last century, become to-day split into three almost isolated branches of enquiry. It is natural that the inherent human bias towards mechanism should have led some men into the belief that much could be learned of life by studying the structure of plants and animals. Their task was a comparatively easy one. The mechanical principles involved in the arrangement of parts were readily appreciated and an ample mechanistic vocabulary was available for their description. The science of pure morphology has had its triumphs. It has accumulated masses of descriptive details of the structure of a vast array of forms both of plants and of animals. But should the pure morphologist be under the impression that by diligently pursuing his studies he will ever come nearer to an understanding of life he is destined to be disappointed. Should he make some revolt against the dominance of purely mechanical interpretations of structure he will find to his cost that the tyranny of mechanistic orthodoxy will cause his opinions to be regarded as suspect by his fellow morphologists. The student of living things who attempted most wholeheartedly to escape from the tyranny of mechanistic thinking was the physiologist ; and the youngest member of the trinity is the psychologist. Orthodoxy has permitted to both the physiologist and the psychologist a certain licence in vitalistic or teleological thinking. Teleology is defined in the *Oxford English Dictionary* as " The doctrine of final causes, view that developments are due to the purpose or design that will be fulfilled

by them." To be a teleologist, therefore, is to believe that developments—in this case, the adjustments of parts and tissues of living organisms—are due to the purpose or ends that they will ultimately serve. Possibly the only snare in accepting such a doctrine of final causes is a purely verbal one. "Purpose" is often, though incorrectly, accepted as involving some implication of consciousness; and "design" is open to the criticism that it may be taken to imply the presence of a designer lurking in the background. To avoid the ambiguities involved in the use of the words "purpose" and "purposive," C. S. Myers (1932) introduced the terms "direction" and "directive," and E. S. Russell (1945), by following this usage, has doubtless stereotyped the employment of these terms in this connection. With these verbal safeguards we might declare a belief in teleology to consist in an acceptance of a creed that developments of the organism are directed towards the ends that they will serve. Stated in this form, the doctrine of final causes does not appear to be a thesis impossible to accept, if only we can perform the strangely difficult feat of securing some measure of emancipation from the all-pervading dominance of mechanistic thought. That the thesis is not impossible of acceptance, and is not even considered as unorthodox in certain biological studies, is a generally recognised fact. No student of psychology need fear that, because he describes some type of animal behaviour as a development directed towards the ends that it serves, he is in danger of having his work condemned as being teleological and so unorthodox. No physiologist, even in the days when he was a student of vital function and not merely a bio-physicist or bio-chemist, ever had to recoil under the stigma of being accused of teleological thinking. It is on the morphologist almost exclusively that the prohibition is imposed. No morphologist is permitted to believe that structural developments of the organism are directed towards the ends that they will serve. It would seem that we are approaching a conclusion that can only rank as absurd, for if the "development" displayed by the organism is behaviouristic or physiological it is permitted to regard it as directed towards the ends it will serve: but should it be structural (morphogenic) then such a supposition is regarded as heretical nonsense and stigmatised as teleological. The common snail, during periods of rest, seeks a flat surface and, by the secretion of its slime, cements the edges of the mouth of its shell to the surface on which it rests. Should a flat surface not be available, the snail will secrete its slime so that it forms a complete diaphragm across the mouth of its shell and so seals it up completely. In the arid areas of Australia there are snails that construct these opercula so thick and made of such resistant material that they persist through years of drought while the animal remains torpid and sealed up within. Some molluscs do not effect this sealing up by behaviouristic or by physiological methods, for they make opercula from their own bodies as part of their normal structure and of this the horny front door of the common winkle is a familiar example. Other molluscs go further and develop elaborate and often very

beautiful calcareous front doors on their own bodies which they draw into the mouth of their shell as they contract. Of this development the well-known "cat's-eyes"—the opercula of certain tropical molluscs—are familiar examples. Moreover, when certain tropical molluscs die, their empty shells are taken possession of by hermit crabs and these crabs have one claw developed into a rounded boss which becomes a perfectly fitting operculum that closes the mouth of the shell as exactly as did the true operculum of its former owner. From a host of other such cases we may select one more that has been so aptly described by Russell and this time naked bodied worms provide the material for study. A naked worm (*Polydora*) may creep about and ultimately find some chink or crack in an oyster shell in which it may conceal itself. Or it may, like *Terebella*, build itself an elaborate protective jacket of fragments of shell and grains of sand cemented together by a secretion provided by the animal. Or like *Hyalinocia*, it may, by physiological processes, secrete material to form a calcareous tube in which its body is protected. Finally, it may adopt an altogether different method and develop a hard resistant cuticle and even a hard protective armament of excrescences on its own body.

Surely it must be admitted that it is frankly absurd to attempt to dictate thought so as to permit us to regard the behaviouristic and physiological activities of the mollusc and the worm as being developments directed towards the ends they will serve and yet to stigmatise as unorthodox and ridiculous the claim that the morphogenic activity is also directive. We are permitted to believe that the snail secretes its operculum and the worm constructs or secretes its protective tube as a directive activity. But to account for the horny or calcareous operculum developed as part of the mollusc's body, or for the thickened and protective cuticle of the worm we must, if we are to be orthodox, postulate that some chance variation was begot at random in some individual and, by the agency of so-called "natural selection," was perpetuated and accentuated until, after untold æons of time, it at length became of some use as a protective mechanism to the animal.

The doings of the molluscs and the worms are merely two examples of a universal truth that the satisfaction of a need may be achieved by the living organism in a variety of ways. They illustrate the omnipresent tendency of living things to effect "developments directed towards the ends that they will serve." A living organism may satisfy a need by some overt behaviour directed towards attaining its end. Or it may attain this end by some functional means which is purely physiological, though not manifested as overt behaviour. Or again, it may satisfy its need by some morphogenic development of its own living structure. It seems that thought must be unduly held in bondage by the dictates of scientific orthodoxy if we are permitted to believe that behaviouristic and physiological activities are directive, but are forbidden to claim directiveness for morphogenic developments. That structural changes are brought about by the haphazard development of chance variations, selected by outside agencies for survival if bene-

ficial and condemned to elimination if not, is the orthodox, or Wallace-Darwin thesis. The mollusc's operculum and the worm's protective cuticle we are assured by orthodoxy "were formed little by little by a series of accidental variations, each one of which was thrown for, as it were, with dice." The expression is Samuel Butler's and he adds that "we shall most of us feel that there must have been a little cheating somewhere" before the animal became so great a winner. Though no orthodox biologist doubts the action of natural selection, even he should be permitted to add the proviso that such an adherence to the Wallace-Darwin thesis of evolution does not preclude a belief that natural selection must have something better than "an almost infinite series of small pieces of good fortune" to act upon. This something better is the development of structural changes begot of function and directed towards the ends that they will serve.

The day is passed when the zoologist, having leanings towards teleological views of life and living, need apologise for his attitude, or defer in humility to the opinions of those who uphold the orthodoxy of mechanistic and materialistic scientific views. It is easy to understand that in the immediate post-Darwinian days it needed a great deal of courage for a zoologist to declare his belief in purpose (or direction) in life processes. Ernst Hæckel proclaimed the orthodox view with loud-voiced authority and the majority of British zoologists fell eagerly into the ranks of those who marched confidently behind him. In 1876 he pronounced his dictum for the guidance of his followers:—"I maintain with regard to this much talked of 'purpose in nature' that it has no existence but for those persons who observe phenomena in plants and animals in the most superficial manner." \*

Here is a dictum typical of the man, of the time and of the prevailing mechanistic mentality. It is small wonder that those zoologists who had leanings towards more vitalistic views, refrained from expressing them in the meetings of scientific societies. But the loud-voiced assurance has passed away: only the tyranny of the traditional mechanistic orthodoxy remains.

It would seem that we have every assurance in believing that all the evidence derived from the study of the behaviour, the life processes and the anatomy of living things leads us to the assumption that all

\* In arriving at a fair judgment concerning any of the dogmatic materialistic statements made by Ernst Hæckel and in estimating the value of his accusations of superficiality on the part of his opponents, we must not overlook the incident, now commonly forgotten, in which, forty years ago, it was publicly stated that he had "taken drawings of other biologists and altered them—taking away fifteen or sixteen vertebræ from one monkey embryo and altering the name, and adding tail vertebræ to another. He also added to a human embryo eleven vertebræ not in the original drawing." When Hæckel pleaded in defence of his action that "the great majority of all morphological, anatomical, histological and embryological diagrams are not true to nature, but are more or less doctored, schematised and reconstructed," even his professional colleagues in Germany found it difficult to support him. Forty-six biologists, representing twenty-five German and Austrian Universities, issued a statement repudiating his claim that scientific usage sanctioned the deliberate falsification of figures purporting to represent actual stages of embryological development.

vital processes, be they behaviouristic, physiological or morphogenic, are directive. We are free to admit, and even to take pride in the admission, that, within these limits, the doctrines of the older vitalists have been fully confirmed by more recent researches. The views of the great anatomist in whose honour this lecture was founded were always forthrightly expressed. Struthers was a vitalist of the vitalists, and writing four years after the publication of the *Origin of Species*, he discusses the condition of the toes of the seal and the walrus, in which animals, as he says, "the internal digit undergoes great teleological development." \* The advent of the doctrine of chance variations selected for survival by outside agencies did not cause Struthers to shrink from declaring his belief in teleological developments.

### THE INHERITANCE OF ACQUIRED CHARACTERS

The conception of vitalism and teleology so far discussed apply to the life activities of the individual organism; but, in any more comprehensive review of the realm of living things, it is necessary to see how far these conceptions may be carried into the question of heredity and so into the summation of the hereditary processes that culminates in changes in the realm of organic life. In considering this extension of our quest we again encounter the antagonisms of our ingrained leanings towards mechanistic imagery and thinking, and the conception that life is a thing apart and that the manifestations of life as living function are the mainsprings of action producing changes in structure. There are those more mechanistically minded biologists who are innately prejudiced towards explaining the changes known to have taken place in the long history of living things by an appeal to random alterations in structure; and those who are more inclined towards explaining the happenings in nature by reference to function. Should it be granted, as I believe it must, that many and important structural changes are brought about as developments directed towards the ends they serve, it must be admitted that it would seem reasonable to expect that these changes might be handed on in the hereditary story of the creature in which they are developed. Such has always been the belief of those who, not being professional scientists, are collectively known as the ordinary man. It would also be confidently expected that the accumulation of these directive developments, handed on in successive generations, accounted for those changes that have been observed in the paleontological records of living things and that form the basis for a belief in organic evolution. Such was assuredly the opinion of the earlier evolutionists who gave first place to function in the production of change in the realm of life.

No matter what popular opinion upon the subject may be, no zoologist to-day would claim (as so many did in 1859) that Charles Darwin was the originator of the conception of evolution, as a thesis opposed to the doctrine of special creation and the fixity of species.

\* "A Variation in the Number of Fingers and Toes, and in the Number of Phalanges, in Man." *Edin. New Philos. Journ.* (New Series), July 1863.

Many had been before him in the field, and, apart from somewhat ambiguous statements of the conception revealed in the writings of certain classical and oriental philosophers, there were the very definite pronouncements made by men whose works were readily accessible to all zoologists at the time when Charles Darwin published his *Origin of Species*. Buffon (1707-1788), Hunter (1728-1793), Erasmus Darwin (1731-1802) and, above all, Lamarck (1744-1829) had all left in their writings the clearest evidence of their understanding of the reality of evolution as a factor in shaping the world of living things. Concerning these older evolutionists, there is no doubt as to their attitude—all were functionalists and all believed in the inheritance of acquired characters. Erasmus Darwin speaks for them all when he writes (1794):—"From their first rudiment, or primordium, to the termination of their lives, all animals undergo perpetual transformations, which are in part produced by their own exertions in consequence of their desires and aversions, of their pleasures and their pains, or of irritations, or of associations: and many of these acquired forms or propensities are transmitted to their progeny."

Functional evolution and heredity was a well-documented and clearly-expressed thesis more than half a century before Wallace and Charles Darwin made their pronouncements upon the origin of species. How then does Charles Darwin stand among the exponents of evolution? Was he, like his grandfather, an advocate of functional evolution? There can be no doubt whatever that Charles had an innate tendency to think of the happenings in nature in terms of function. More than twenty years before his first publication on evolution, he reveals clearly the shape that evolutionary ideas were taking in his mind. In his *Beagle* diary he wrote in 1834:—"Nature, by making habit omnipotent, has fitted the Fuegian to the climate and productions of his country." But in 1839, when he published his edited journal, he altered the passage, and, in its final form, it appears as:—"Nature, by making habit omnipotent, and its effects hereditary, has fitted the Fuegian to the climate and productions of his miserable country." This is Lamarckianism pure and simple and there is no doubt that he owed more to his grandfather than any possibly inherited bias in his manner of thinking upon matters related to changes brought about in living things. He was acquainted with his works on evolution and, what is perhaps even more important, was familiar with the works of Lamarck very early in his questings concerning the fixity or mutability of species.\* It is apparent that he started his thinking on evolution

\* The first notes made on the subject in 1837 were entitled "Zoonomia" (the title of his grandfather's work). The notes were amplified in 1844 (after he had read Malthus) and concerning them he tells Hooker (11th Jan. 1844) that in their making "I have read heaps of agricultural and horticultural books," etc., and mentions the work of Lamarck, with some disparagement. It is remarkable that only six months afterwards (July 1844), he wrote to his wife concerning the fate of these notes in case of his death and asks that "my sketch should be published as it is, stating that it was done several years ago and from memory without consulting any works." Francis Darwin (the editor of the *Life*) adds as a footnote to this letter that the words "several years ago and" were added at a later date.

on functional lines and remained to the end of his days a believer in "the inherited effects of the use and disuse of parts." But in his last pronouncements on the subject he gave to these inherited effects of use and disuse no more than an "important" rôle in aiding the effects of "natural selection of numerous successive, slight, favourable variations." These slight variations were random structural variations—"each one of which was thrown for, as it were, with dice"—and in expressing his belief that evolution had been "effected chiefly" through their agency, Darwin ranks himself among the advocates of structural evolution and heredity. From the study of Darwin's own writings it seems to be true to say that when first he made any speculations on the question of evolution, he did so with the mental outlook of a functionalist. A functionalist he remained to the end of his days; but something happened to persuade him that random structural variations acted on by natural selection must be given some place in the business. Just what the relative importance of these two factors in the whole question was, he never resolved in his own mind: at one time he placed the one first in importance and at another he adopted the alternative explanation. There can be no doubt that it was the reading of Malthus on *Population* that impressed him so strongly with the reality of the struggle for existence, that he became torn between his old beliefs in the inherited effects of use and disuse and his newer ideas of the struggle for existence causing, what he termed "natural selection" to eliminate unfavourable, or preserve favourable, random variations of structure. Even after he had become impressed by the works of Malthus he still remained a believer in functional evolution and heredity; and Huxley noted that in his first essay on evolution—written in 1844—"much more weight is attached to the influence of external conditions in producing variations and to the inheritance of acquired habits than in the *Origin*." One other thing happened before his publication of the *Origin* in 1859, and that was the arrival of Alfred Russell Wallace's paper "*On the tendency of varieties to depart indefinitely from the original type*." Wallace gave no encouragement for any belief in the functional views of the older evolutionists and so, when the *Origin* appeared, the functional aspect of evolution and heredity was mostly subordinated to the doctrine of the "Struggle for Existence" resulting in "Natural Selection" determining the fate of chance variations of structure. But though 1859 marks the time when Darwin gave maximum weight to structural evolution and heredity, he never abandoned his earlier belief in the influence of function, derived from his own natural mental outlook and from an acquaintance with the works of his grandfather and of Lamarck.

It was unfortunate that the publication of the *Origin* created so profound an impression upon the scientific and unscientific alike that, without pause for considering the historical facts of the case, Darwin was acclaimed (and condemned) as the original propounder of the thesis of organic evolution and of the falsity of the doctrine of special creations and the fixity of species. Darwinism, or Darwin's theory,

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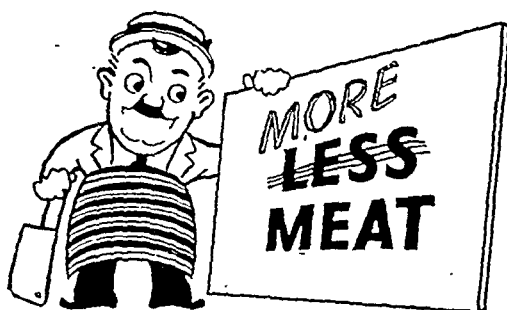
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was widely accepted as being synonymous with the doctrine of organic evolution.

It was not until after the clamour had died down that the voices of the few, who justly claimed that Buffon, Hunter, Erasmus Darwin and Lamarck had all been before him in accepting the general facts of organic evolution, made themselves heard. The truth of this could not be gainsaid and it became obvious to Darwin's advocates that, if his claim to originality were to be sustained, it must be on the ground that he (with Wallace) had originated the theory that natural selection, acting on chance variations, accounted for the mutability of species and the progress of evolution. It was therefore necessary that the functional (or Lamarckian) details included in the work of Darwin should be thrust into the background. It was also desirable that these views should, if possible, be demonstrated as erroneous, thereby leaving the natural selection theory in sole possession of the field. "Darwinism," which had been so widely accepted as the synonym for evolution itself, must, when this position was no longer tenable, be regarded as the only true explanation of the observed phenomena of the process of evolution. The matter was made more simple by the publication, in 1885, of Weismann's *Theory of the Continuity of the Germ-plasm*. Darwin had been dead three years before Weismann's book appeared, but he had been a correspondent of the German biologist for some years before his death. It is significant that Wallace was one of the first British biologists to embrace Weismann's doctrines, and there was remarkable unanimity among orthodox scientific men in accepting Weismann's views and in declaring that the inheritance of acquired characters was an absolute impossibility. The discussion of evolutionary changes was purged of its functional elements. Lamarckism had received its death blow. There was only one true teaching—the doctrine of natural selection, begot of the struggle for existence, acting on random structural variations.

From that day to this, Weismannism has had wide acceptance as a verity. The belief in the possibility of the inheritance of acquired characters has been ranked as a scientific heresy and such as have showed a leaning towards this belief have been stigmatised as teleologists and regarded either as cranks or as persons uninstructed in modern orthodox science. Nevertheless, any biologist who is prepared to re-examine Weismann's work with an open mind must be forced to the conclusion that his thesis is no longer tenable. Briefly, Weismann's theory claimed that germ plasm and somatoplasm are separate and independent entities, or, in his own words, "The splitting up of the substance of the ovum into a somatic half, which directs the development of the individual, and a propagative half, which reaches the germ-cells, and there remains inactive, and later gives rise to the succeeding generation." Germ plasm is derived from previous germ plasm and so is distinguished by its continuity: and it cannot be derived from, nor influenced by the vicissitudes of, the discontinuous somatoplasm. This concept naturally culminates in the claim:—

"The familiar fact that the excision of the reproductive organs in all animals produces sterility proves that no other cells of the body are able to give rise to germ-cells; germ plasm cannot be produced *de novo*." The thesis was rather a crude concept and it demands no elaborate analysis to reveal the falsity of Weismann's claims: it will be enough to state, in the briefest possible form, a few facts upon which general agreement may be expected from all biologists: (1) In the whole realm of unicellular organisms the germ plasm and somatoplasm, if they be indeed separable entities, must be combined in the single cell that constitutes the entire organism; (2) The propagation of plants from slips or cuttings, or even from isolated leaves, in which there is presumably no germ plasm, is a familiar piece of knowledge; as is also the fact that plants so propagated produce the so-called germ plasm in their seeds when they become mature. (3) Not only plants, but multicellular animals, such as the common hydra, may be propagated by regeneration from small parts of the body which cannot be supposed to contain germ plasm and the reconstructed animals produce sex cells in the ordinary way. Lastly (4) the most fatal objection of all; even the higher vertebrates such as birds and mammals are capable of producing new sex cells (presumably from somatic cells) after complete removal of the original gonads. The conclusion must surely be that Weismann's theory is so patently vulnerable that it cannot possibly prohibit the acceptance of the thesis that germ plasm can be produced *de novo* by all living things and that since this is so, there is no reason whatsoever to believe that germ cells are so aloof from the ordinary body cells as to remain absolutely uninfluenced by the vicissitudes which affect the body as a whole. If we are free to admit the possibility of this, there is no reason why we should refrain from a re-examination of the whole question in order to assess the value of the opinions put forward by the older, pre-Darwinian, evolutionists. In order to do this, it is necessary to have agreement of two points: (1) What is meant by an "acquired character"? and (2) What factors would be likely to influence the question of its inheritance? We will define an acquired character as "a feature developed during the life of the individual possessing it, in response to the action of use or environment" (Doncaster), and we will quote Charles Darwin in agreeing that "several generations must be subjected to changed habits for any appreciable results."

Adhering to our definition, we are free to disregard the pathetic reiterations of the futile claims of those experimentalists who have tried to interpret the ways of nature by taking upon themselves the rôle of the Divinity that shapes our ends. Man has mutilated his domestic animals for centuries. He has cut off the tails of dogs and sheep and horses for his pleasure, but he has not thereby produced tailless pups or lambs or foals. The initiatory rites of Semitism have been in vogue for a far longer period and yet they have produced no structural alteration in the Jewish babe. These things, along with the ridiculous experiments performed on mice by Wiesmann and by present-

## FREEDOM OF THOUGHT IN SCIENCE

day genetics on fruit flies, constitute a large part of the armament of those who defend the thesis of the impossibility of the inheritance of acquired characters. But to regard the docking of dogs, or the performance of the Jewish ritual, as being something "developed in response to the action of use or environment" is to so gravely misunderstand the point at issue as to call for nothing more than summary dismissal from all consideration of the question.

Concerning Charles Darwin's claim that "several generations must be subjected to changed habits for any appreciable results" there is more to be said. A complete disregard for the factor of time in the consideration of experimental evidence is almost universal, and is doubtless due to the human vanity begot of man's ability to effect rapid changes in the development of his machines. Man has changed the structure of his engines so profoundly that the transition from "Puffing Billy" to the jet-propelled plane has occupied the lifetime of only a few generations. Surely that human ability to effect progressive changes in the vast complexity of his machines cannot be baulked by an organism so trivial as a fruit fly (*Drosophila*)? Such a mechanistically begot assumption of power by man to effect changes in nature according to his will must be responsible for such common statements as that culled from the work of a very recent writer on evolution:—"Nor need we pay attention to the view advanced by certain Lamarckians, that the inherited effects of functions or environmental modifications are so slight that they cannot be detected experimentally but require cumulative action through thousands of generations to become obvious. Exceedingly minute differences can be detected by proper technique. The total failure of sixty-nine generations of disuse to affect the eyes or the phototropic responses of *Drosophila*, is a good example of the failure of disuse to produce Lamarckian effects" (Julian Huxley, 1942). The sobering effect of studying the long story told by the examination of geological deposits has fortunately saved the paleontologist from falling a victim to this human vanity. "There is apparently no directly proportional relation between the rate of succession of generations and the rate of evolution, and genetic experiments based on this assumption may be based on a series misconception. It is perhaps worth mentioning that a species of the genus *Drosophila* existed in the Upper Eocene about 45 to 50 million years ago" (F. E. Zeuner, 1946). Since the maximum rate of evolutionary change that has been detected by paleontological studies is "about 500,000 years per species step," we need be concerned no more with the vanity of the laboratory experimentalist who declares that because his short-term experiments have failed to show that acquired characters are capable of being inherited the whole thing is impossible. It may seem, perhaps, a little presumptive to reject a reasonable thesis by opposing the human experience derived from breeding sixty-nine generations of fruit flies to the 500,000 years or so that nature has expended upon the production of a differentiation sufficiently marked as to be deemed worthy of specific distinction among

elephants. Once and for all, the advocate of the orthodox mechanistic school of thought in heredity and evolution should renounce the argument that his failure to demonstrate its happening is proof of the impossibility of its occurrence. Having taken this necessary step towards clearing the issue, it is possible to consider some instances in which characters, acquired originally in response to the action of use or environment, do in fact appear to have entered ultimately into the heritage of the animal.

It is a familiar fact that air-breathing vertebrates that are aquatic in their habits, swim at the surface with the head held so that the nostrils, eyes and ears are above the water line. The precise alignment of nostril, eye and ear is conspicuous in such diverse forms as the hippopotamus, the seal and the crocodile. If a terrestrial animal, such as a dog, takes to swimming, it attempts to produce this alignment by throwing its head back. It is necessary that the long axis of the face should be extended in the same direction as the long axis of the body. To attain this position, the cervical region is bent backwards and the cervical portion of the vertebral column becomes extended so that it is convex on its ventral aspect. The dog, during the occasional exercise of its powers of swimming, is producing, as a temporary posture, what thoroughly aquatic mammals have achieved as a permanent modification. No one doubts that the seals were derived in the very distant past from some type of carnivore that lived a normal mammalian terrestrial life. It is natural to assume that, at the very outset of their departure from normal terrestrial life, the ancestors of the seals produced the characteristic curvature of the cervical region only when actively engaged in swimming. It is a further justifiable assumption that, as aquatic life became more habitual, this peculiarity became increasingly impressed on the disposition of the cervical vertebræ. In the end, it became a definite and permanent feature of the adult. Fortunately, in this case, we know more than that. In 1910, Marett Tims described the embryos of Weddel's seal collected during the Antarctic voyage of the *Discovery*. Of these embryos, he says:—"The most interesting point which I have observed is the extraordinary downward curve in the cervical region of the vertebral column." The point was interesting since the curve of the cervical region of all other mammalian embryos is in the opposite direction. The cervical portion of the vertebral column of the embryos of normal mammals is flexed—in the seals it is extended. Marett Tims did not (perhaps wisely) postulate that the peculiarity of the cervical region of the seal embryos was due to the inheritance of a character originally developed in its ancestors in response to the action of use or environment. Yet if we are prepared to divest ourselves of all prejudices begot by the inculcation of Weismann's doctrines, I think we must admit that this is the only reasonable explanation of the facts.

We are dealing, in the case of the seals, with an instance in which a posture, habitually assumed by an animal in response to a functional demand, produces some alteration in its structure. This alteration

may, in its initial stages, be merely a temporary one, maintained only so long as the posture is assumed. But with long continuance of the habit through time, measured only in geological terms, the postural modification becomes more and more impressed upon the structure of the animal and so persists, not only while the posture is maintained, but as a permanent feature of the adult animal. Finally, the modification becomes manifest in the absence of the stimulus that originally invoked it and, as a part of the structural make-up of the animal, it becomes passed on in the hereditary characters of the species. Free from the influence of Weismann's doctrines and from the bondage of structural mechanistic thinking upon the question of heredity, we are at liberty to postulate that it was in this way that the bent neck of the seals, begot as a temporary posture in response to use and environment, became incorporated into the normal congenital characters of the animal. We may believe that such an account of the happening is a reasonable one. Or, orthodoxly, we may believe that the occurrence of a chance variation (by which some carnivore with a leaning towards swimming was born with a slightly bent neck) became perpetuated and accentuated by the action of so-called natural selection. Or again, we may take refuge in that glorious compromise known as organic selection "according to which modifications repeated for a number of generations may serve as the first step in evolutionary change, not by being impressed upon the germ plasm, but by holding the strain in an environment where mutations tending in the same direction will be selected and incorporated into the constitution. The process simulates Lamarckism but actually consists in the replacement of modifications by mutations" (Julian Huxley, 1942). This thesis is simply an example of the specious verbalism prevailing in modern science. Modifications, being somatic, cannot be inherited; but mutations, being germinal, can be, according to orthodox views. When a modification is inherited it is, therefore, necessary to say that it is a mutation. By some strange alchemy a modification goes on being a modification "for a number of generations" and then gives place to a mutation "in the same direction." Quite legitimately we could translate this dictum as: "acquired characters (modifications), by oft-repeated recurrence in a very large number of generations and after the passage of an enormous period of time become mutations and so are incorporated into the heritage of the animal." This does not simulate Lamarckism; it is Lamarckism.

The case of the bent neck of the seals is cited merely because it is such a gross and conspicuous example of a structural modification, due to posture, having become part of the normal heritage of the animal. Moreover, it is especially instructive, since certain anatomical features suggest that the sea lions and the true seals may have arisen independently from different ancestors among the early and primitive carnivores. These primitive carnivores were numerous and well diversified at the very dawn of the Eocene period, say, 70 million years ago, and the seals were fully perfected during the Miocene—a matter

of some 30 million years ago. It is not too generous an allowance of time to suppose that 40 million years or so were available during which the modification of the neck was becoming part of the heritage of, possibly, two different stocks of carnivores that had a fancy for swimming and for finding some of their food in the sea.

There is no need to discuss in detail the innumerable other cases of postural modifications that have become built into the heritage of animals. The callosities of the African wart hog and of many other animals are well known ; and it is equally well known that these things are present in the embryo long before they will ever be called on to protect the underlying tissues against pressure produced by some peculiar habit or posture. The facets developed between the lower end of the tibia and the distal end of the talus in those human races that sit in the hunkered, squatting position, simply cannot be explained away by any modern verbiage : and it is the same with the many other instances of modifications produced by habitual posture. It is not only with posture, but in connection with innumerable trivial, though oft-repeated habits, that this same truth is demonstrated. It is beyond doubt that many mammalian hair tracts are developed by the toilet habits of the animal ; and it is equally beyond doubt that the peculiar disposition of the hair is present as soon as ever hair develops in the unborn embryo. It is needless to continue this survey. We will return to Erasmus Darwin and, with him, declare that "From their first rudiment or primordium, to the termination of their lives, all animals undergo perpetual transformations, which are in part produced by their own exertions in consequence of their desires and aversions, of their pleasures and their pains, or of irritations, or of associations : and many of these acquired forms or propensities are transmitted to their progeny."

The effects of long-continued and oft-repeated posture or habit, which seem so clearly to become ultimately incorporated into the structural heritage of animals, are examples of "use inheritance." But the older evolutionists, and pre-eminently Erasmus Darwin and Lamarck, entertained no doubt that the effects of disuse could be inherited in exactly the same way. Even Charles Darwin, when it suited his purpose, invoked the inherited effects of disuse to account for the presence of certain vestigial structures. His attitude upon this question is typical of his duality in thinking upon evolutionary changes. His method of dealing with the problem of the wingless beetles of Madeira is a good example of his alternations of belief. The reduction of wings, he affirms in one passage, is clearly the result of "natural selection," since "those beetles which most readily took to flight would oftenest be blown out to sea and perish." It was to this passage that Samuel Butler made his characteristic rejoinder :—"Mr Darwin cannot mean that the fact of some beetles being blown out to sea is the most important means whereby other beetles come to have smaller wings—that the Madeira beetles in fact come to have smaller wings mainly because their large winged uncles and aunts—go away."

But Butler's devastating criticism did not dispose of the matter, for Darwin, in another passage in the same work, declared his belief in the inheritance of the effects of disuse, for he wrote "it is probable that disuse has been the main agent in rendering organs rudimentary," and applies this agency to the case of "the wings of beetles living on small and exposed islands." Such a pronouncement, and many other passages in the *Origin* give whole-hearted support to the doctrine of the inherited effects of disuse—a truly Lamarckian conception; for Lamarck himself had written: "long continued disuse in consequence of habits which an animal has contracted, gradually reduces an organ, and leads to its final disappearance." \*

Struthers, true to the best tradition of Scottish anatomists, was a pioneer in studying the anatomy of the cetacea. It was he who gave us the complete description of the anatomy of the humpback whale. It was he who described the trivial remnants of the pelvic girdle and hind limbs concealed deep within the tissues of the body. He realised that the tiny remnant (a slight rudiment of a pelvis and a femur 4 inches long in an animal measuring 40 feet) could have no possible function; but was merely the remains of an originally functional limb that had lost its function from disuse. He says:—"It might be looked on as serving a sesamoid function, but it does not play on cartilage and does not give the mechanical advantage of a sesamoid. It has even less muscular connection than the small oval femur in my 50 feet long *B. musculus*. *Mysticetus* has also a rudimentary tibia, *Megaptera* a femur only, *B. musculus* a still more rudimentary femur, and *B. borealis* as I find, none at all." † How did the fully developed hind limbs of the ancestors of the whales come to be represented merely by some ridiculously misshapen remnants in their modern representatives? It is indeed possible to imagine that, since whales had become thoroughly adapted to an aquatic life, and had developed a new mode of progression through the water by movements of the specialised caudal extremity, their hind limbs became redundant and useless. It is also possible to imagine that these redundant hind limbs, by protruding from the otherwise stream-lined body, might be an actual impediment in making progress through the water. It is here that "natural selection" is invoked to eliminate those whales that had more perfectly

\* It seems strange that Darwin, who expressed so frequently views that are frankly Lamarckian, should have resented any suggestion that his theories owed anything to the influence of Lamarck. On 12th March 1863, he wrote to Lyall: "Lastly you repeatedly refer to my view as a modification of Lamarck's doctrine of development and progression. If that is your deliberate opinion, there is nothing to be said, but it does not seem so to me. Plato, Buffon, my grandfather before Lamarck and others, propounded the obvious view that if species were not created separately they must have descended from other species, and I can see nothing else in common between the *Origin* and Lamarck. I believe this way of putting the case is very injurious to its acceptance, as it implies necessary progression, and closely connects Wallace's and my views with what I consider, after two deliberate readings, as a wretched book, and one from which (I well remember my surprise) I gained nothing."

† *Memoir on the Anatomy of the Humpback Whale*, *Megaptera longimana*. Edinburgh. MacLachlan and Stewart, 1889.



developed, though useless, hind limbs. That is reasonable enough, if we are persuaded of the reality of this agency, and we might picture "natural selection" acting until finally no hind limb is left projecting from the body. But that is not the end of the process, long after the hind limb ceased to be represented as an external appendage, it shrinks within the tissues of the body so that, as Struthers determined, *Mysticetus* has a rudimentary pelvis and a femur and tibia. *Megaptera* has a rudimentary pelvis and a slight remnant of a femur and *Balaenoptera borealis* has even lost its femur. No stretching of the theory of "natural selection" can account for the reduction of the limb once it has ceased to be a projecting member and an impediment to progress through the water. "Natural selection" cannot, so to speak, pursue the diminishing hind limb into the depths of the tissues of the body.

It is so with all diminishing and disappearing organs rendered useless by change of habit or environment. To some it may seem most reasonable to suppose, as the older evolutionists supposed and as Charles Darwin postulated, when it suited his purpose, that the atrophy of the organ is due to the inherited effects of disuse. Modern science accounts for the phenomenon by the simple expedient of an appeal to a formula of verbal jargon. The hind limb of Struthers' humpbacked whale was in the condition in which he found it because it was "rendered vestigial in the adult by being endowed with negative heterogony" (Julian Huxley, 1942). It may be that this verbal formula solves the whole problem of dwindling structures that are no longer of any use in the life activities of the animal. But with the mental bias that has, perhaps mistakenly, guided us through this brief essay, it seems more simple, and quite in accordance with observed facts, to suppose that these things are clearly expressions of the truth of the doctrine of the inherited effects of disuse.

Now it is commonly laid to the charge against those misguided people who persistently believe in the doctrine of the inheritance of acquired characters, that they are ignorant of, or that they take no account of the well-proven findings of the modern Weismann-Mendel-Morgan school of geneticists. Should this charge be made in this instance, let us be quite clear on one point. No attempt is made to account for the fact that one species of lady-bird has twelve spots and another has three upon its elytra. We are not concerned with the fact that one species of Burnet moth has five spots on its fore wing and another has six. We do not care if one species or subspecies differs from another by some minor detail of colour, pattern or proportion. The great law of the inheritance of acquired characters and of the directive nature of adaptations does not concern itself with the least. These things may safely be left to the short-term investigations of the modern geneticist. There is room for more than one factor, and for more than one vehicle, of hereditary characters in the great story of the changes that have taken place in living things. The making of the wonderfully adapted anatomical changes that result in the production

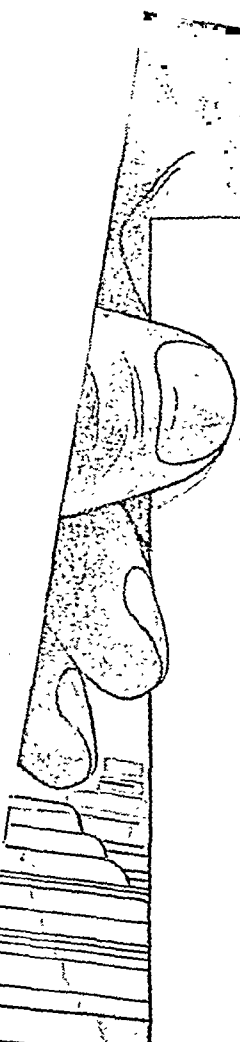
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of a perfected seal, need not be, and surely is not, due to the same agency, nor is it carried by the same vehicle of heredity, as is the development of an added spot on the elytra of a lady-bird. The follower of Lamarck does not disregard the work of the modern geneticist nor does he stigmatise it as being impossible or absurd; but he has the right to ask that the modern geneticist should refrain from ridiculing the doctrine of the inheritance of acquired characters just because this question defeats any sort of solution by his man-made, short-term experiments. There is plenty of room, both for the Lamarckian and for the Weismann-Mendel-Morgan geneticist in the great quest for the truth regarding those known changes which have taken place in the realm of life, that give rise to the doctrine of organic evolution.

The purpose of this lecture is in reality a plea for a return to the freedom of thought that prevailed a century ago when Struthers was teaching anatomy to students in Edinburgh. It is a plea for the freedom of the teacher to speak of life and of living things in terms that definitely imply that he regards life as something peculiar and distinct from the conditions prevailing in the inorganic realm of lifeless matter. It is a plea that, in doing this, he should not be charged with inculcating mysticism, or of having a leaning towards dealings with metaphysics. It is a plea that he may speak of the innate directiveness of all living processes, without incurring the charge that he appeals to some anthropomorphic dictator of purpose. It is finally a plea that he may be free to believe and to teach that "a feature developed during the life of the individual possessing it, in response to the action of use or environment" may, after constant and long-continued repetition, and over an enormous period of time, be ultimately incorporated into the inheritance of its descendants. All these pleas may be granted without infringing the patent rights of any of the more modern schools of thought, and there is no reason whatever why we should not return to that heyday of comparative anatomy marked by the freedom of scientific thought that permitted John Struthers to inspire a succession of students in Edinburgh and Aberdeen.

# ON DEPRESSION

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## INTRODUCTION

MUCH of general medical practice is taken up with what are loosely called functional disturbances. Many of these functional disturbances are emotional in nature and psychiatric in origin and therefore require psychiatric investigation and treatment. In most instances this psychiatric investigation and treatment is a matter for the family doctor and the general physician, and not primarily for the specialist in psychiatry.

The surgeries of general practitioners and the out-patient departments of general hospitals are often visited by patients who are worried, anxious or depressed, and who have multiple bodily complaints not indicating organic disease. Although an emotional upset may be the essence of the patient's disability, the presenting symptom is often a bodily complaint. The patient may be worried because he fears his bodily complaints indicate serious disease. There may be no evidence of organic disease. In many such instances, reassurance that all is well, added to the confidence instilled by a careful physical examination, will permanently relieve the patient of his anxiety. This is a simple matter of everyday practice.

In other instances, the bodily complaints appear excessively out of proportion to any minor bodily ailments which may be present, or the symptomatology is more obviously psychiatric, neurotic or otherwise, and the patient is not nearly so easily reassured or helped. Such a patient is often demanding, and the physician is sometimes at a loss to know how to investigate further and what lines of treatment to pursue.

Such disabilities occur frequently in general practice. The analysis of the statistical returns of casualties among troops in the two wars has done much to bring home to us what a large amount of medical disability is dependent on psychological factors. Many emotional disturbances among soldiers diagnosed in the first world war as shell-shock, or disordered action of the heart, were in the second world war better understood as anxiety neuroses or anxiety-depressions, and, as a result, were better treated. Various estimations, both among troops and in civilian practice, suggest that not less than a third of all patients seeking medical help do so for essentially psychiatric disabilities. This is a very large proportion.

Confronted by such large numbers of patients suffering from

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## ON DEPRESSION

emotional disabilities, which are time-consuming to investigate and difficult to come to grips with, it is not surprising that many doctors feel that there is not much to be done about such patients, that they are not seriously ill and that psychiatry has little to offer towards their treatment. There must be few of us, psychiatrists included, who have not felt at least a slight heaviness of spirit at seeing the woe-begone face of the chronic hypochondriac yet again in the waiting-room. This defeatist attitude to the clinical challenge of these patients is of course an evasion of the difficulty. On the other hand, one certainly cannot blame the busy practitioner if he wishes to conserve his time for the patients whom he feels he can help most. It is true that some patients are so constitutionally loaded and so hemmed in by morbid emotional attitudes and by adverse social circumstances that they are difficult to help. Yet many patients with psychiatric disabilities can be greatly helped and in quite simple ways.

## MORBID DEPRESSIVE STATES

The opportunities for helpful therapeutics among patients with these psychiatric disabilities can be well illustrated from a consideration of morbid depressive states. A great deal can be done for depression. It is not depressing therapeutically.

It was Adolf Meyer who proposed that the word depression should be used to designate all those unpleasant affective states grouped under the term melancholia. The advantages of this change in nomenclature are that the word depression conveys the essence of the mood disturbance of melancholia, draws attention to its similarities to ordinary human unhappiness, does not suggest, like the word melancholia did, that the mood disturbance is a disease entity, and is such a general term that it obviously requires amplification. It therefore tends to encourage enquiry about the various factors which produce the disturbance in each instance.

There are two main ways in which a patient with depression can be investigated. They are complementary and both should be employed. First, the illness can be classified according to its course and symptomatology as an example of a particular disease. Here we are thinking in terms of the clinical group to which the illness appears to belong. Each clinical group has its broad implications as to prognosis and treatment. Secondly, the illness can be investigated as part of the life story or biography of the patient and as an example of his adaptation to life. Here we are thinking in terms of the interplay between the constitutional tendencies, personal emotional drives and environmental stresses. An understanding of the relation between the illness and the patient's adaptation to his life situation supplies a more individual and personal appreciation of diagnosis and prognosis and of possibilities of treatment. Morbid depression can take many clinical forms. It can occur either alone or in association with, or as a complication of, some other

illness, whether a bodily illness or a mental disorder. It is often associated with anxiety, and indeed anxiety is often part of the depressive reaction. The clinical pictures of depressive states, their settings and their causes, vary greatly. The mildest forms of depression may be indistinguishable from ordinary human unhappiness and discouragement. Such is a universal human experience. The classical picture of severe morbid depression is that which Kraepelin designated manic-depressive disease. The classical features are sadness and hopelessness, inability to feel affection and love, difficulty in thinking, retardation, dearth of ideas, preoccupation with a few topics, self-criticism, self-blame, self-accusation, ideas of punishment, grave risk of suicide, and important bodily symptoms, namely: sleeplessness taking the form of early morning waking, loss of appetite, loss of weight, loss of sex desire and amenorrhœa; the whole worse in the morning and tending to lift a little in the evening. The illness often occurs without any obvious precipitating factors and runs its course to complete recovery. The attack may recur or alternate with mania. Constitutional and hereditary factors are strong and important. Manic-depressive disease tends to occur in persons of pyknic physique—the round sturdy John Bull build—and of syntonie or warm-hearted well-adapted personality. The illness runs in families. Partially dominant Mendelian genetic factors undoubtedly predispose to its appearance. Manic-depressive disease is strongly hereditary, constitutional, endogenous, characterised clinically by severe depression, suicidal thoughts and marked physiological disturbances.

In estimating the nature and severity of an individual instance of morbid depression it is useful to compare the clinical picture with that of classical manic-depressive disease and with that of ordinary human unhappiness.

Perhaps the most frequent type of morbid depressive illness is one characterised by mild depression and anxiety symptoms. Such an illness often occurs seemingly in response to a difficult life situation. The patient often comes to the physician complaining of some bodily symptom. He keeps the more personal and emotional matters in the background. The presenting symptoms are frequently headache, constipation, indigestion, abdominal pain, fatigue, lassitude, loss of weight, backache, precordial pain, menstrual irregularities and sleeplessness. Some of these symptoms when they occur together quite strongly suggest the presence of insidious organic disease. It is therefore not surprising that in general hospitals these depressive patients are found in the first instance more often in the medical or surgical departments than in the department of psychological medicine.

#### CLINICAL EXAMPLES

I should like to cite some clinical examples of morbid depressive states where the presenting symptom is a bodily complaint.

## ON DEPRESSION

A man aged 50 complained of moving sensations in the epigastrium, belching, acid regurgitations and palpitation after food, of one year duration. Electrocardiogram, test meal and barium meal showed no abnormality. He was referred to an ear, nose and throat department for his complaint of mucus falling at the back of his throat. A dental surgeon advised total extraction of teeth. He was then referred to medical out-patients' at Guy's Hospital where, in addition to his bodily complaints, more definitely emotional symptoms were observed. He was a proud man, a former company sergeant-major in the Royal Marines, and was struggling with and trying to hide symptoms of deep depression, tears, morbid gloomy thoughts coming unbidden to his mind, lack of interest in himself and in his wife, loss of interest in food, early morning waking and depression of activity so that he could not make himself do a day's work. This patient had not mentioned his depressed feelings because he was both ashamed of and afraid of them. He had instead stressed minor bodily symptoms which in normal mental health would probably not have been the subject of complaint.

A woman aged 42 with symptoms of involutional melancholia was first examined in hospital for her complaint that her throat was stopped up so that she could not swallow. Her complaint was a depressive delusion.

A former soldier aged 34 presented with epigastric pain immediately after food, lasting a few minutes and relieved by alkalies. A barium meal X-ray showed no abnormality. He also complained of a sharp digging pain below the heart, excessive mucus in the throat and a dull heavy feeling in the forehead made worse by reading. The left maxillary antrum was opaque to X-ray but an antral wash-out was clean and there was no evidence of infection of the respiratory tract or lungs. His symptoms were all of two years' duration, since his return home from the army, and were worse when he was staying at home and not working. Further questioning disclosed anxiety symptoms, guilt feelings and brooding shame about a venereal infection contracted in the army. Cure of his infection had not relieved his guilt and some residual testicular pain kept up his anxiety. Treatment consisted quite simply of insisting on the absence of organic disease, in explaining the nature of anxiety symptoms, in encouraging him to think more of the future and to live more for his wife and children. The whole family have recently had a happy holiday at the hop-picking.

The following case report shows a more complicated symptomatology and etiology.

A skilled carpenter aged 41 had three severe attacks of eczema all occurring, interestingly enough, at times of serious social difficulty in his life, the last attack following the destruction of his home and belongings in a London air raid, an event which has inflicted constant domestic difficulty and financial stress on him during the last four years. His eczema has not cleared up. After being off work for



twenty weeks he was reduced in seniority, position and pay from a job which he greatly valued and in a firm in which he had worked for fifteen years. Following a period in hospital in an unavailing attempt to cure his eczema he complained of marked loss of interest in everything, inability to get going, sleeplessness, and on examination he showed a psychotic retarded depression with ideas of reference. His mother had suffered a depression for two years in middle age.

The points I wish to stress in this biography are the piling up of deprivations and losses over years coupled with an inability to do much about the situation. In addition to these environmental stresses there is the possibility of an inherited constitutional tendency to depression. His depression was removed by five electroplexy treatments and arrangements were made to get him a more senior job with consequent increase of his morale and some relief from his financial burden. He has remained well.

A married woman aged 39 presented with epigastric pain of recent onset associated with many anxiety symptoms arising out of an unhappy domestic situation. There was tenderness over the duodenum and a barium meal X-ray showed a spastic irregular duodenal cap. Recently she had been depressed, tearful, sleepless, had thought much of suicide, had lost interest in her home and had given up her part-time job. Admission to hospital relieved the domestic situation and allowed suitable dietetic treatment and attention to her sleeplessness and depression. The domestic situation was discussed with her husband and readjustments made with the help of a social worker.

The case shows the interrelation of anxiety, depression and possible duodenal ulcer, the necessity in treatment to deal with the total life situation, her bodily health, her interpersonal relationships and her environmental stresses, and also shows the value of social workers as medical auxiliaries.

The following two case reports illustrate the association of depression with minor bodily ailments.

A man aged 47 came to hospital with a right-sided parotitis somewhat resistant to treatment. It was noticed he was unduly preoccupied with his painful face. Further investigation showed that, although he had a long history of good skilled work, for the last seven months he had shown depression, sadness, tears, feelings of inability to carry on, ideas of self-blame and lack of interest in life and hobbies so that, a keen gardener, he had let his carnations die.

A woman aged 44 came to medical out-patients' with severe headaches which had bothered her in attacks since the age of 17 but had been more frequent and more severe in the past five years. The headaches were migrainous, one sided, violent, associated with vomiting and some prostration and relieved by ergotamine. There were signs of hypertension, a blood pressure of 190/105, but no cardiac enlargement or failure and no urine abnormality. Formerly

a bright cheerful person, since her mother's death five years ago she had become chronically depressed with constant low spirits, sleeplessness and difficulty in looking after her house and children. It was clear that but for her emotional depression she would not have specially complained of the headaches she had borne for so many years.

### RECOGNITION OF DEPRESSION

The loss of weight, lassitude and alimentary disturbances so frequent in depressions prompt a search for organic disease. Examination may reveal no definite evidence of such possibilities as cancer or tuberculosis. Findings such as a raised blood pressure, a glycosuria or radiological evidence of osteo-arthritis of the spine do not fully explain the symptomatology. A tentative diagnosis of organic disease may be made, or the disability considered to be "largely functional," but the true nature of the disorder is often not appreciated.

There are many reasons why mild depressive states are sometimes not recognised. The physician as a result of his training is preoccupied with the problems of organic disease. Insufficient acquaintance with the clinical picture of severe morbid delusional depression makes it more difficult to recognise depressive symptoms when they occur with only moderate severity and along with bodily complaints. The physician may not be in the habit of making any systematic enquiry into a patient's emotional state and personality problems. He may feel that such enquiry is an intrusion on the patient's privacy and he may therefore not like to make it. If abnormal emotional reactions are observed the physician may have some difficulty in appreciating the extent of their morbidity because of lack of trained experience.

Sometimes depression is the last symptom of which the patient complains. Patients tend to stress their bodily complaints because they believe that their bodily symptoms are their illness, or because they think that a doctor is a person who deals with bodily disease and is not interested in emotional feelings. Moreover, people are shy of speaking of their feelings. Sometimes in depressive states the feelings are so grim that the patient dreads to mention them.

After the bodily complaints have been investigated, if the patient is asked how he feels about life in general and in his spirits in particular, he will begin to talk of his real problems. The bodily complaints can then be seen to occupy a relatively minor part of the total clinical picture. Such findings as a dominating sadness, a loss of feeling, a loss of activity, suicidal thoughts, early morning waking and a morning-evening variation in severity make the diagnosis plain. If the physician can question the relatives he may obtain a keener appreciation of the great change in mood and in behaviour which has taken place.

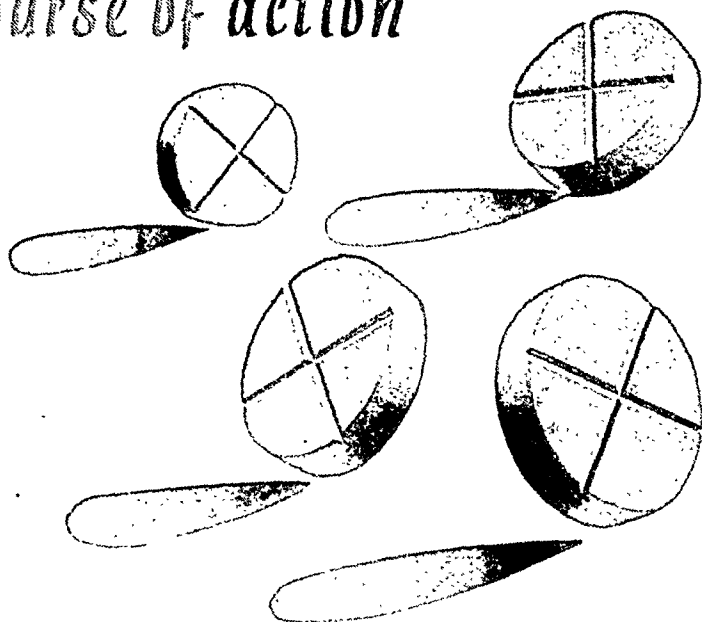
## PSYCHODYNAMICS

The psychodynamics of depression—that is, its nature and how it works—are slowly becoming better understood. Depression, in the sense of ordinary human unhappiness or low spirits, arises from a loss or deprivation of some valued object or situation. The well-known commercial advertisement, "He won't be happy till he gets it—Pear's Soap," indicates that frustration, combined with an inability to overcome that frustration, causes depression. These observations on the nature of depression received support from investigations made into the factors determining morale in troops of the armed forces. Among factors favouring good morale are a feeling of personal value, a sense of comradeship with other members of the regiment, a group or team spirit and other factors, which need not be specified here, more directly related to the business of war. "Broken" troops, that is troops who have lost leadership, group spirit and a sense of worth-whileness tend to be depressed in the sense of being unhappy, inactive, lacking spontaneous initiative or interest in doing something for themselves. They have suffered a loss. One of the most powerful factors destroying the morale of the individual soldier was unfaithfulness of the married partner at home. A soldier's realisation of the loss of the love of his wife often produced a bitter sadness, a withdrawal from social activities into silent preoccupation, that is, a state of depression.

But there is a more fundamental basis of morale, namely the supply of food and warmth. This is trite and true. Obviously one of the easiest ways of making a man depressed is to make him cold, wet and hungry and to give him no hope of being anything else. "When food is done and the hope of food is gone then sets in a dreadful gloom," in the words of a distinguished combatant officer who had much experience of deprivation in the Burma jungles. Poor and hungry people are often unhappy and somewhat inert. It may be that depression of spirits and of activity is the normal human biological reaction to chronic unavoidable burdens such as bad cold housing and inadequate food. Loss of freedom, love, honour or worldly goods are some of the many possible deprivations. In estimating the personal effect of such deprivations it is essential to find out how much the objects are valued. This is one aspect of the psychodynamics of human unhappiness.

Mourning over a bereavement is the classical example of normal depression. It is a highly personal affair. The mourner is sad, finds the daily tasks of his life an effort and is unable to make new emotional attachments. But it is clearly a reparative process. Readjustment of emotional values takes place usually in about three months and the mourner returns to normal enjoyment of life. The relationship of mourning to melancholia since Abraham's fundamental paper, supplemented by Freud, has produced a psychoanalytic theory of the

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**CASE HISTORY:** E. S. Housewife aged 72 years. Varicose ulcer of 27 years duration upon antero-lateral aspect of lower  $\frac{1}{3}$  left leg. (Fig. 1.)

**TREATMENT:** June 21st. Area of ulcer 56 sq. cms. Elastoplast applied as follows:—

No dressing to ulcer. Stirrup from head of fibula along lateral side of leg, under sole and up medial aspect of leg to level of tibial tubercle. Long strip from tibial tubercle along anterior surface to base of toes. Elastoplast applied as continuous circular turns from base of toes to tibial tubercle enclosing heel, each turn overlapping the preceding one by  $\frac{2}{3}$  of its width. (Fig. 2.) One and a half bandages were required and were applied as tightly as possible by hand. Patient instructed to perform normal household duties.

**PROGRESS:** June 28th. Area 56 sq. cms. Ulcer base clean. Odour far less objectionable. Elastoplast reapplied as before. Patient seen at fortnightly intervals. Area of ulcer calculated at each visit. Elastoplast reapplied as before.

July 21st: Area 30 sq. cms. Odourless.

September 1st: Area 7 sq. cms.

November 3rd: Area  $\frac{1}{2}$  sq. cm.

November 24th: Ulcer healed. Total duration of treatment 22 weeks. (Fig. 3).

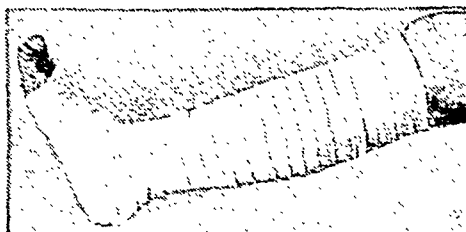
**FURTHER TREATMENT:** December. Elastic stocking supplied.

February: Juxtafemoral ligation and retrograde injection of left internal saphenous vein.

*The details and illustrations above are of an actual case. T. J. Smith & Nephew Ltd., of Hull, manufacturers of Elastoplast, publish this instance—typical of many in which their products have been used with success.*



Fig. 1



Above Fig. 2

Below Fig. 3



## Fundamentals



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nature and origin of depression. Without necessarily subscribing to any of the theoretical interpretations, it is possible in many instances to see how the concatenation of the forces of nature and nurture have produced the morbid state.

All depressions arise from the interplay of personality and environment. Loss of valued and loved objects produces normal depression. The easier the depression is produced by such losses presumably the stronger the constitutional weakness or inherited tendency to this reaction type. Clinical facts support this view. In some instances, either because of the environmental strain of accumulative losses or because of the power of an inherited tendency, or because of both together, something happens whereby the depression ceases to be wholly reparative but develops also a morbid influence on the organism. There is an analogy with the physiological process of inflammation which, although reparative, may become malignant.

The histories of patients suffering from depressive illness often show many unhappy events and circumstances, bereavements and other losses, which appear to be related causally to their depressions. It seems that a sense of personal worth, a sense of personal value to the other members of the family or to the social community, identification with a cause or an ideal, and, especially, the experience of loving and of being loved or the serenity of religious faith, are some of the anchors of happiness. Certainly clinical practice shows that when such emotional experiences are destroyed unhappiness supervenes. But, clinical examination also indicates that rarely do such losses of themselves cause morbid depressive illness.

Morbid depression is differentiated from normal depression only by its occurring either without any apparent cause or by being excessive in quality, quantity, and duration, in the circumstances in which it has arisen. These criteria are obviously inexact. They must be so. Clinically there is no sharp division between normal and morbid depression. Although a mild unhappy state in which it may be profitable to tell and help the sufferer to cheer up, is quite different from a delusional psychotic depression which has passed out of conscious control, yet clinically it is easy to find patients who show all gradations of normal and morbid depression between these two extremes. It is therefore understandable that the events and circumstances which produce normal depression are often found contributing to morbid depression.

These various events and circumstances all have in common that they involve a loss of or a failure to gain what the patient values in life. They comprise an absence of the joys of life. It is customary to look upon such environmental factors as precipitating factors of the illness, and so to relegate them to a less important place in the psychodynamics of depression than personality and constitutional factors. This does not seem justifiable. Such environmental factors are present in a large proportion of cases, 82 per cent. in a recent survey of 100 consecutive cases of mild depression. The proportion

tends to rise the more fully patients are studied, and what they value, find good, and crave for, is appreciated.

The troubles of daily life tend to become more obvious as dynamic factors as life gets older and the resilience of youth recedes. This is probably the explanation of the high incidence of environmental factors in involutional depressions and the depressions of later life.

When environmental factors are particularly prominent the depressive illness has been thought of as a resultant reaction to these factors. Lewis has demonstrated the fallacy of this conception and the impossibility of separating depressions into two contrasting groups, reactive and endogenous. Yet the idea of a reactive depression dies hard. The trauma judged sufficient to produce it would be such as might be expected gravely to upset the average healthy person. But healthy people have very great powers of adaptation and recuperation, as the experience of war showed. They are more upset by long-lasting stresses than by violent catastrophies. Such chronic stresses are less prominent in the clinical history than sudden dramatic happenings which are too often blamed for depressive illness. If a patient reacts violently to apparently minor events this is not reactive in the above sense of the word, but indicates that the patient was sensitised by past experience to these events which had special significance for him. The criteria of reactivity are previous good health, a close time relationship to the supposed cause, adequacy of this cause, a thought content of the psychosis directly related to the supposed cause and the disappearance of the psychosis when the cause is removed. Lewis points out that adequacy of the cause is a matter of opinion and he found that very few, if any, depressive psychoses fulfil the criteria. A close time relationship is not necessarily a causal relationship. Moreover, memory and anticipation annihilate time so that events of past years may remain vivid in the mind and dynamic in the production of symptoms. It frequently happens that the more carefully the patient is examined the more environmental factors are found. The difficulty in classifying patients into reactive and endogenous groups depends not only on the extent to which the case is investigated, but also on the interpretation of the findings. Reactive depression as a special sub-group is therefore not a helpful dynamic conception.

Gillespie used the word reactive in a rather special sense which is more dynamic and more therapeutically helpful. He assessed reactivity not only by the importance of precipitating environmental factors in producing the illness, but also by the response of the patient to external events in his past life, by his reaction to environmental changes in hospital while suffering from his illness, by his reaction to changes in his internal environment such as his reaction to good or bad nights of sleep, and finally by his accessibility to psychotherapy. His reactive depressions were clinically psychoneurotic, and in this way different from his endogenous depressions, but he admits that there is much overlapping of his clinical groups.

In another and more true sense all depressions are reactive. The waning of the early Kraepelinian conception of disease entities at the hands of Kraepelin himself, the growth of a more dynamic outlook, and the increasing interest in personality, constitution, and heredity, led Meyer to formulate his conception of reaction type. The idea that a human being reacts to a given set of circumstances in terms of his past experience, personality and make-up, is a psychobiological one, and implies that the reaction is purposive and adaptive. Such accords well with the orthodox conceptions of medicine and general biology. It is easy to see the reparative nature of many depressions, and it is a clinical fact that a patient after a depression may be for years in better mental health than ever before.

### INVESTIGATION OF THE PATIENT

In the case of any mental disorder, major or minor, it is often helpful and time saving to get a history of the illness from the patient's relatives before one sees the patient. It is always advisable to check and amplify the patient's story in a later interview with members of his family. In this way not only are the patient's difficulties more completely understood and his life situation appreciated, but abnormal attitudes or delusions are less likely to be missed. The more relevant information that can be obtained from the family the more possible it is to estimate accurately how the patient's behaviour has changed from what was his normal, and also to judge the attitude of the relatives to the patient, their reaction to his illness and their ability to help or to cope with the situation. "What do you notice wrong with your husband? How did it begin? How is he different from his normal self?" Such questions as these may prompt the story. Many people have difficulty in describing the deficit or absence of activity so often a feature of depressive illness. A detailed description of just exactly what the patient did and said from the time of waking onwards through the day and night will go far to elicit the objective facts about the amount and kind of spontaneous activity and of sleep, topics of conversation or of special preoccupation and concern, interest in self, in food and in friends and social recreation. A recital of the day's activities will often jog the memory for the odd, abnormal or unhappy things the patient did and said.

It is important to note the attitude of the relatives to the patient's illness. Have they tried to cheer him up, to take him out of himself, to take him on a holiday? Have they been critical and unhelpful, telling him to pull himself together? The possibility of insanity in a near relative is always distressing. Some relatives eagerly seek medical advice and tell the story frankly and fully. Others, when confronted by insanity, try to explain away, push aside, ignore or deny the terrible facts: they want reassurance so much that they may suppress unpleasant facts in the hope of getting it. This understandable attitude



refers particularly to the patient's threats of suicide. "He does not really mean it; he just talks silly at times." The physician is well advised to be insistent in enquiry into such matters.

Before seeing the patient, and later from the patient, it is convenient to obtain some brief facts about his previous mental and bodily health, his activities and enthusiasms in work, home, hobbies and recreations. Such information will enable the physician to assess what assets and resources the patient has to fall back on in his illness. The mental health of the family should also be enquired into.

A history of the illness from the relatives will enable the physician to appreciate better the patient's attitude to his difficulties and to come quickly with the patient to some of the topics of chief concern. All mental disorders have social reverberations. An appreciation of the situation from the relatives' point of view is essential if one is to deal helpfully and constructively with the social complications of the illness. Many lay people still think that a doctor's job ends with the bodily examination and treatment of his patient. They doubt if difficulties and failures in the home and in the job are matters for medical enquiry. The physician must not expect much spontaneous information on these points.

The patient should be examined alone, certainly not in the presence of members of his family. He is likely to talk more freely of his troubles in private. Note taking is essential. The symptoms are so varied, so entwined with the life history, and so personal to each patient, that the busy practitioner cannot keep the essential facts in mind unless some written record is made at the time of examination. The record need not be lengthy. The ability to recall quickly the main points about a patient's life, the exact nature of his job, the names and ages of his children, tend to increase confidence in the physician. A short scheme of the main topics to be enquired into is a useful aid to memory, but an elaborate *pro forma* of all the points which can be covered tends to restrict a real understanding of the patient.

The examination should begin with the patient's complaints. In the case of emotional disorders the usual question "What do you complain of?" may be supplemented by modifications such as "What do you feel wrong?", "In what ways are you not yourself?" The complaints should be recorded in the patient's own words. They are likely to be multiple. "What else?" should be a frequent question. The patient is likely to mention first his bodily complaints as he thinks them of more medical interest than his feelings.

The complaint of depression requires further elucidation. Patients vary greatly in their use of this word, and often mean by it something quite different from the physician's conception. "What does it feel like? Can you describe it more? How does it affect you?" or, more bluntly, "What do you mean by depression?" are useful questions. Patients sometimes describe pure anxiety symptoms or phobias as "depression." Similarly, a complaint of headache calls for more exact description. In depressive illnesses "headache" is often not

head pain but a sense of weight or fullness in the head, or a more mental symptom of difficulty in thinking, or mental gloom.

Once the symptoms of the illness have been recorded the patient should then be examined physically to exclude or confirm the presence of intercurrent or associated bodily disease. By this time the patient will have gained confidence so that a more detailed examination of his worries, fears, preoccupations or topics of concern can profitably be taken up. The Anglo-Saxon race tend to hide their feelings and have some difficulty in expressing them in words. Facial expression and movements of the hands will often convey much about the emotional state. The topic of emotion may be approached by such questions as : " How are your spirits ? " or, better, " How do you feel in your spirits ? How do you feel about all this ? What do you feel like doing about it ? " or, more concretely, " What are you going to do about it ? How much does all this get you down ? Does it ever reduce you to tears ? " In cases of mild depression it is often helpful to ask what the patient thinks about and how he feels when he lies awake in the early morning. The main content of his thoughts and his chief topics of concern will have appeared in the patient's story of his illness. Abnormal or delusional attitudes may be further elicited by questions such as : " What do you think about most of the time ? What sort of thoughts run in your mind ? What do the family think about you ? Do you think they are right ? Who is to blame ? " The question of suicide should be frankly discussed. The topic may be approached by such questions as " Have you thought it worth while to carry on ? Have you felt that life is not worth living ? What have you felt like doing about it ? " An intentionally vague question such as " What about death ? " may produce an illuminating response. The patient should then be asked bluntly if he has thought of ending his life. If so, it is important to find out if he has got the length of considering ways and means to suicide, and if he has the means available or has in fact attempted his life. The examination may be concluded by enquiry about previous health, previous attacks of emotional disturbance, and by the recording of the main biographical facts about the patient's life, work, family, responsibilities and recreations.

### DIAGNOSIS

The diagnosis of the existence of a morbid depression is not difficult. The elucidation of its causes is another matter. The first step towards diagnosis is to remember the possibility of the disease. Morbid depression is often overlooked, both in its mild and severe forms. The diagnosis is easy once delusions have appeared. Mild depressions present more difficulty. Confronted by a syndrome of fatigue, loss of weight, sleeplessness and some emotional disturbance, it is right to think of insidious organic disease, but examinations for such are carried too far when, in spite of negative results, the search

# SURGICAL PRACTICE IN SCANDINAVIA

## SOME IMPRESSIONS OF A RECENT VISIT

By M. R. EWING

WHEN the would-be surgical traveller turns the pages of his atlas and plans his wanderings, he finds his choice infuriatingly restricted. In these days of dollar shortages and the devalued pound, journeying in the New World is the privilege of the few. The hard-currency areas nearer home are little more accessible, and as he contemplates the map of Europe he will find few countries indeed which are not either tightly closed against the enquiring visitor, or which seem likely to satisfy his searching, if not for newer things, at least for a better use of the old.

Thirty or forty years ago he would certainly have made for Vienna or Berlin or Heidelberg or Tübingen. Excluded from all fruitful contact with surgical progress during the course of two world wars, and busied meantime with the more pressing problems which follow complete economic disruption, German and Austrian surgeons have ceased, for the time being, to make the impressive contributions to surgical knowledge, which in earlier generations brought them fame and made their clinics centres of international pilgrimage. Italy, trying hard to cover up the ravages of her recent disastrous trial of arms, is ill-equipped to play the part of host, and a journey to Spain means for most of us, the repeated humiliation of failure to make ourselves even imperfectly understood. Eastern Europe we can for the moment discount: we are left with France and the Low Countries and the progressive Scandinavian capitals.

Now Scandinavia has much to attract the surgical visitor. Where previously the practice of medicine was closely linked to the teaching of the German schools, contact now is almost exclusively with the west. The Swedish surgeon of the younger generation speaks fluent English and crosses the Atlantic for his postgraduate education. His senior, for whom German was the first language in his schooldays, is busy trying to match the fluency of his junior colleague. He does little to renew earlier contact with his once esteemed mentors in the former Reich, and a bright new American textbook of operative surgery finds its place on his bookshelf beside an old edition of Kirschner. This affinity with the surgery of the western world seems likely to endure and even to become more close—for reasons economic and political, no less than medical. English is spoken everywhere and with a patient toleration which is a constant delight to the British visitor.

Written while holding the Paterson Travelling Scholarship of the University of Edinburgh.

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But if Scandinavia seems now in surgery to look to the west, her surgeons come not only to learn and to take away, but also handsomely to give. For have not our northern colleagues in these past twenty years or more made some most impressive contributions to the practice of surgery? I was fortunate enough in Örebro to watch an arterial embolectomy, proudly and rightly described as a "Swedish operation," and is it not from Scandinavia too that we have learned so much of venous thrombosis, of heparin, and of dicoumarol, and in still more recent times of the adventurous surgery of the heart and great vessels.

Here, too, we have a friendly and highly intelligent community enjoying for the most part a very high standard of material comfort and with an enviable record of progress in hospital planning and construction. Add to this the delight of a stay in a most attractive country, and the not inconsiderable comforts of a food-laden table, and we surely have inducements enough for the intending traveller. Nor is he likely to be disappointed. Surgeons come visiting from every corner of the globe. In Stockholm I met Americans and Canadians, New Zealanders and Australians, and travellers from almost every nation in Latin America, as well as from India and Pakistan. Every country in Europe west of the Iron Curtain was represented and of the Poles I met at least one was not a political refugee.

For the British surgical visitor in Stockholm one of the first delights will be exploration of the glorious new hospitals of which she is so proud. Built, many of them, while we were engaged on the grim business of systematic destruction, each is a model in painstaking and yet imaginative planning. The vast Södersjukhuset is a 1200-bedded city hospital built on a glorious site on the south side of a rocky island where it slopes down to the water's edge. The view from the solarium out across Lake Malaren is a tonic indeed. If from the outside its clean design suggests more the modern factory than the traditional infirmary, its interior offers to patient and staff alike a degree of comfort which must be the envy of all. There is everywhere an abundance of space, wide well-lit corridors and halls and broad stairways, and a complete absence of the dark corners which make so many of our own hospitals look, however clean, so dirty and so dreary. So much space allows work to go on efficiently and quickly, so that there was completely absent that untidy activity with which we are so familiar, and which gives a false impression of productive busyness. A highly efficient communication system, a multiplicity of high-speed lifts, both large and small and an ingenious system of floor and departmental numbering, helps to off-set the spatial disadvantage of such a huge hospital. It was interesting to see what great pains had been taken, by the close grouping of the various consultation and diagnostic units to ensure the easiest collaboration between the various departments. Largely to suit the convenience of the diagnostic service the hospital functions as two distinct 600-bedded hospitals, each served, for example, by its own X-ray unit. If there is any substance in the argument that

such a huge hospital has no more of the personal touch than is offered to the mass-produced car as it moves along the assembly line, every patient at least enjoys the privacy of a ward which never holds more than two. The light, adjustable beds, all mounted on large quietly-turning wheels, make transportation everywhere so easy and so comfortable! Trolleys and all the tiring and painful liftings which their use involves, are rarely required. The shocked patient, transferred to his bed in the theatre, can from the very start be kept in the head-down position by simply raising the lower end of the wire mattress.

The theatres are furnished with a shining array of stainless steel, which is, in fact, found everywhere in abundance. One was impressed by the operating tables where every change in position and in tilt, can be controlled from the head end of the table with none of the customary fumbings under the towels or under the table which seem with us so often to be the necessary preliminaries to any change in position. Large, efficient anæsthetic screens and a useful assortment of simple table fittings to control the position of the arms and to maintain that of the trunk, also caught the eye.

In general, anæsthesia outside the larger teaching units falls far short of the high standard of excellence we seem now in our hospitals almost uniformly to enjoy. Efficiently as the nurse anæsthetist often seems to do her work, one felt very often that the job for the surgeon was being made unnecessarily difficult. It is little wonder that he turns to local and to spinal anæsthesia, but I did not enjoy the spectacle of operations under spinal anæsthesia made easy by the completely flaccid abdominal wall, but only at the expense of a grey, cold, sweating patient whose systolic blood pressure had gone tumbling down to disturbingly low levels.

If one is sometimes tempted to believe that our surgical colleagues in Scandinavia work less hard than is the custom over here, one must admit that not only are they off to a much earlier start in the morning, but also that they have learned to use their working hours more efficiently. The flow of cases to the theatre is a continuous one, a feature which abundance of space and an ample staff makes easy of attainment.

Dictaphones are a feature of even the smaller hospital and type-written records are almost the rule. Occupied or not, they are always most generous with their time, and I had the happy experience of enjoying for very long periods the company of many of the busiest surgeons.

I was most impressed by the excellence of the diagnostic radiology. An admirable practice, which is an established morning institution in most of the Swedish clinics, is the joint morning meeting of the entire surgical staff with the radiologist, when all the films of the previous day are set out on lighted racks and reviewed together. This affords an admirable opportunity for profitable discussion and for teaching, an opportunity which I must admit, seemed not always to be turned to full advantage. The high quality of the films presented is due, in part

no doubt, to the excellent modern equipment which seems everywhere to be available and to the prodigal use of films of which there is no apparent shortage. There is, however, no question that the roentgenologist is stimulated not only to take great pains to present to his colleagues only first-rate films, but also to scrutinise them most carefully before he offers them for public inspection. He is, in fact, quite definitely put on his mettle and no doubt the surgeon is equally keen on occasions to catch him out. In his interpretation of the X-ray findings there is no question that he must get great help from this discussion with his surgical colleague and also by reference to a full case summary which is always at hand. It is only at the end of this joint consultation that the report is made (and this into the dictaphone which is always to be found waiting patiently nearby).

It did seem to me sometimes, that the excellence of the X-ray work had led the clinician to place an undue reliance on the findings of his colleague, a tendency which is, of course, by no means peculiar to Scandinavia.

It was in the Soder hospital that I first saw in Scandinavia, operative cholangiography, which is now in many clinics almost the routine. The cannula was as a rule inserted into the stump of the cystic duct, after removal of the gall-bladder and the exposure was taken as the opaque medium was being injected. With the cassette already in position, to swing the tube over the wound was a matter only of a few moments: changing the film was equally easy and there was little risk at any stage of soiling the operation field. With a dark room available in the theatre suite the film was quickly available, the whole performance taking, as a rule, no more than 7 to 10 minutes. One was impressed by the good quality of the films and on at least one occasion where the gall-bladder was empty of stones and when none could be felt in a dilated common duct, a row of negative shadows seen in the hepatic duct proved on subsequent exploration to be due to numerous facettted biliary calculi. It was the practice in some clinics to repeat the cholangiogram 8 to 10 days later. Any stones overlooked at operation and then displayed were dealt with by Pribram's method. It seems that the discomfort which follows the instillation of ether is very variable and can be relieved somewhat by giving a quick acting antispasmodic. On close questioning one had the impression that this line of treatment was followed more because it was the best available and not in the expectation that the stones would in fact be dissolved.

Biliary disease is very frequent in Sweden. I found no fewer than five cholecystectomies on the list one morning. The frequency of cholecystitis is noticeably high in all surgical clinics and it was the opinion of several clinicians that the incidence of cholelithiasis is rising steadily. Certainly in one small provincial hospital serving a closed population of 30,000 or thereabouts, the chief surgeon had found the number of biliary operations to be increasing steadily each year, although



he had changed in no way meantime his criteria for surgery. I was surprised to find that retrograde removal of the gall-bladder is not uncommon, a method which is believed to lessen in the hands of the inexperienced the risk of damage to the common duct and the right hepatic artery. In Örebro, I watched Professor Bohmansson use an unorthodox exposure of the gall-bladder area. A curious U-shaped cut is made over the right costal margin, the open end of the U being directed medially. The rectus is reflected back from its insertion into the anterior aspect of the lower ribs and the posterior sheath divided below the costal margin. Pains are taken to preserve the ninth intercostal nerve. The incision when repaired is a valvular one, unsuited for drainage, but this is to him no hardship as he has long since omitted what experience has taught him to be quite unnecessary. This incision is said to have the merit of seldom being followed by herniation, but I was not convinced that it gave quite such good access as the Kocher subcostal approach.

It was at Örebro too that I saw demonstrated again how helpful it can be to mobilise the second part of the duodenum by the Kocher manœuvre. It was Bohmansson's custom to do this by simple finger dissection, tearing through the peritoneum along its right margin and freeing its bloodless attachments. Examination of the less accessible parts of the common duct is in this way made astonishingly easy.

Bohmansson is a firm advocate of the Billroth I operation and here too free mobilisation of the descending part of the duodenum is the first step in the operation. Dr Perman, senior surgeon in the St Eriks hospital in Stockholm, when doing a Polya-type gastrectomy moves over to the left side of the table to mobilise the duodenum and tells me that he tackles a cholecystectomy always from this side. Although no doubt by training and practice ambidextrous, he is of choice a right-handed surgeon and finds from long experience that palpation of the common duct along its whole length is much easier from this side. The preliminary mobilisation of the duodenum certainly seemed in his hands to make the turning in of the duodenal stump unusually easy. He is one of the finest gastric surgeons I have had the privilege of watching: I was accordingly the more impressed to learn that a drain passed down to the sutured duodenum is with him routine.

It seemed to me everywhere that surgeons were not entirely happy with the results of mutilating high gastrectomy, in the management of the duodenal ulcer with a high acid curve. The disturbingly high frequency of dyspeptic sequelæ (mostly thought to be due to purely mechanical troubles) is an encouragement to those who favour less radical resections and a protective vagotomy, and I had the unusual experience of watching a Polya being converted into a Billroth I—this in a relatively young woman, who became so faint and uncomfortable after every meal that she was forced to take them all lying down.

There may be something in Bohmansson's argument that one of the important and undesirable effects of a Polya type gastrectomy is the

complete suppression of the reflex and carefully controlled physiological mixing of the duodenal contents with pancreatic and bile ferments. Equally reasonable I found his argument that Nature must have good reason to have sent the tenth cranial nerve all the way from the cerebrum to the abdominal viscera: too good a reason, in fact, to justify one's cutting it light-heartedly at the hiatus without pausing to study closely the effect of its division on structures other than the stomach. Even if such an argument lacks any real scientific value, it has, for me, the virtue of being good common sense. It is only fair to add that he considers the risk of any undesirable side effects of this nerve section no deterrent to vagotomy in the management of the difficult anastomotic ulcer. Vagotomy I did not find in very high favour anywhere, but many are hopeful that they may be able, with its help, to steer a course between the Scylla of the subtotal gastrectomy with its attendant postoperative dyspepsia, and the Charybdis of the less radical resection and its complicating stomal ulcer.

It seems that in Norway carcinoma of the stomach is a very common disease and Professor Holst of the Rikshospitalet in Oslo, was there able to present to the British Thoracic Society a series of close on 70 cases of carcinoma of the cardia which had come to surgery in his own clinic. Despite a gratifying low immediate mortality rate, the distressing digestive symptoms which so often follow these resections and the disappointingly short survival seemed almost to make him question the value of such radical surgery. Professor Crafoord is reluctant to divide the costal margin when doing a thoraco-abdominal resection for a gastric cancer, but the somewhat restricted exposure which this allows in the duodenal dissection, would, I am sure, make the operation for the average surgeon, insufferably difficult.

The Karolinska Sjukhuset, which is the main State hospital in Stockholm, is the centre of undergraduate teaching. It is a comparatively new building, planned on the most generous lines, and is the parent hospital to a group of special units which are being established on the same site. The radium centre is complete and has been in full operation for some years and among others contemplated or under construction are centres for pediatric surgery, thoracic surgery and plastic surgery. The pathological and X-ray facilities are admirable and the hospital group when complete should offer splendid opportunity for co-ordinated teaching. The number of students is small and the amount and variety of clinical material more than adequate. In the latter part of their period of study, the students are given much more responsible duties than is the common practice in Britain. The relatively small number of students does, however, allow of much more careful personal surveillance of their work than would generally be the case with us. On a nearby site, there is growing up a cluster of new buildings to house the various institutes of the medical faculty, and also the library.

The surgical unit at Karolinska is directed by Professor Hellstrom,

well known for his classical contribution on staphylococcal infection in relation to renal lithiasis. Streptomycin here, as elsewhere in Scandinavia, seemed to be freely available, and in Sweden aureomycin was already being given a clinical trial. In prostatic surgery, the Millin approach seemed generally to be in high favour, and for cancer of the bladder, transplantation in two stages with a total cystectomy added to the second was the common practice.

One of the outstanding medical clinics in Sweden is the radium centre or Radiumhemmet. Radiumhemmet, from very small beginnings as a small 16-bed "hospital" in a rented flat established by a far-seeing surgeon as long ago as 1910, has continued to flourish ever since. Five million Swedish crowns, subscribed by a loyal people as a 70th birthday gift to King Gustaf V, was handed over by him to establish a new radiotherapy centre, immediately adjoining the Karolinska hospital. Completed just over ten years ago, it has about 140 beds and a vast out-patient department. It enjoys an enviable reputation and has for many years dominated the field of cancer therapy in Sweden. One is left with the impression (but in this I may well be quite wrong) that in the treatment of malignant disease, surgery appears to play a secondary and somewhat subservient rôle. Certainly patients are referred to Radiumhemmet directly from all corners of the land, without the preliminary screening in a surgical consultation service which is, I believe, a commendable feature of most British clinics. I found it difficult too, to accept the very strong bias against biopsy (at least without previous therapy), but Professor Berven can adduce figures of a lower survival rate when biopsy is used to establish the diagnosis, to support his argument. There can be no question of the high quality of the work which is done here. The follow-up system is a model in efficiency. A free railway journey to hospital from even the remotest corner of the land is one of many measures which help to ensure its completeness. It is in cancer therapy where observation to be instructive must be prolonged and accurate, that careful note-taking is so important and here documentation and filing is admirably handled.

Enjoying as it does an international reputation, the facilities which it offers to visitors are wholly admirable. To follow Professor Elis Berven on one of his conducted ward rounds is a refreshing experience and one is soon infected by his almost boyish enthusiasm and tireless energy. As we moved from bed to bed, I was early struck by the arresting frequency of the Plummer-Vinson syndrome, especially in the women-folk from the country districts of the north and west. Professor Berven and his staff diagnose it, on the first glance from the foot of the bed, and I must admit that I soon came to recognise the pale, thin face, with its small, contracted mouth and angular stomatitis. I have seldom seen such striking clinical manifestations of this syndrome, and there could be no mistaking the atrophied mucous membrane with its associated dysphagia and the deformed nails.

Dr Ahlbom in the radiotherapy department serving the city hospital, sees these manifestations much less frequently. I am told that in the remote corners of Norway, it is uncommon, a fact which some would like to attribute to their generous intake of liver oil from the salt-water fish of the North Sea. Its importance as a precancerous lesion was only too clearly apparent, as one saw it again and again, not only in association with the common postcricoid growths, but with cancer at other sites in the mouth and throat. A striking improvement in the five-year survival rate of postcricoid carcinoma, within recent years, may well be the result of an energetic campaign to bring home to general practitioners the grim significance of the Plummer-Vinson syndrome.

One was surprised to see several young men with malignant disease of the œsophagus. Using many portals of entry and intensive treatment, some very gratifying results have been obtained. Ahlbom's work on the pathology and treatment of mixed salivary tumours is, of course, well known, and I was interested to see a long-standing but apparently benign growth in the parotid coming to surgery after pre-operative radiation. The space left after excision of the tumour along with its capsule was filled by a Mikulicz drain brought out through the middle of the partially sutured wound. This was the preliminary to a radium needle implant a few days later and an ultimate closure of the wound by secondary suture.

The fair-skinned people of the west and north often fall prey to the farmers' cancer, and multiple rodents or squamous-celled tumours are among them a commonplace.

Tumours of the antrum seemed to be frequent and the immediate response to radiation, in most cases, very gratifying. Clinical photographs taken at stages throughout the treatment give a most dramatic index of the progress of the disease.

The use of a children's size urethroscope introduced through the anterior nares, is a method of endoscopy I am keen to try out, in the difficult search for nasopharyngeal growths. Professor Berven has a clever trick in such cases. When confronted with a patient who presents with a hard lump high up in the cervical chain and where no obvious primary can be found, he passes an orange stick tipped with cotton wool through the nostril and along the floor of the nose on each side, until it impinges against the posterior wall. Each is now fairly vigorously rotated. The presence of blood on the cotton wool on one or other side is strong presumptive evidence of the presence of a nasopharyngeal growth.

One was surprised to find here that radical surgery for malignant disease of the breast was still in high favour, the post-operative radiation being considerably less intensive than is the fashion in this country. Radiotherapy is also given on occasion to the "mastitic" breast or to the case with bleeding from the nipple and no detectable tumour, but continued careful supervision of such cases is the rule. In the clinical

examination of the breast, the patient leans slightly forwards and places the palms of the hands on the surgeon's shoulders, a manœuvre which ensures complete relaxation of the axillary fascia.

To a surgeon, the circuit of Radiumhemmet is a most interesting experience, and a sharp reminder of the increasing encroachments on territory which has for long been the preserve of the cold steel blade.

Professor Crafoord's clinic is the mecca of many of the foreign visitors, and as if to show that the restrictions of an old hospital are of little consequence to a surgical genius, he continues to flourish in the old city Sabbatsberg hospital. His attention is now directed almost entirely to thoracic surgery and especially to that of the heart and great vessels. His work in this sphere is too widely known to need more than mention, but to be privileged to follow at close quarters the steps of a Blalock operation completed with a brilliance that is both faultless and unhurried, makes a journey from the remotest corner of the globe seem well worth while. He is very well served here and in his country sanatorium by an excellent team of radiologists, cardiologists and clinical physiologists who produce for him first-rate tomograms and angiograms (helpful often in assessing the operability of a lung tumour), a complete picture of oxygen tension and pressure values in almost every chamber in the heart, selective spirometry and a host of other equally illuminating investigations. It was in this clinic too that I saw most evidence of a keen interest in the laboratory practice of pure experimental surgery.

Docent Sandblom works at the Kronprinsessan Lovisas hospital, one of the only two children's hospitals in Sweden. Like Professor Crafoord, he too, is a brilliant surgeon who has made a close study of the surgery of the heart and great vessels, and here again I was impressed by the close collaboration between physician and surgeon and the excellence and completeness of the investigations of the team of cardiologists.

It is a curious thing that we, in Great Britain, have been so slow in giving a fair trial to the non-operative methods of reduction of the intussusception of childhood. Hipsley and his disciples in Australia, and many Scandinavians (such as within recent years, Hellmer of Lund and Nyborg of the Kronprinsessan) have all published excellent results which compare more than favourably with our best surgical figures. It is not enough to argue that we do not see cases early enough, although I have no doubt that our surgical colleagues in Scandinavia have brought home to the practising physician the urgent necessity of the earliest diagnosis.

The management is, in most clinics, primarily a surgical responsibility, but the majority of patients come to the radiologist not only for a diagnostic enema but for a therapeutic reduction. Roughly half the cases at the Kronprinsessan come to surgery, most of this number being cases where the radiological evidence of complete reduction has been somewhat equivocal. Laparotomy in such cases means no more

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than a quick look through a McBurney incision and in the majority the reduction is found to be, in fact, already complete. No doubt this method requires a high standard of radiology and only the gentlest manipulations ; and most important of all, the confidence that comes from a widening experience.

The high mortality in the infant that attends resection of the gangrenous intussusception has encouraged the practice of exteriorisation. Provided steps are taken to complete the resection and to restore bowel continuity within ten days or so the great risk of serious water depletion and of grave nutritional upset is said to be avoided : any attempt to postpone closure of the ileostomy leads almost invariably to a fatal issue.

One was surprised to find the surgeons here, happily surrendering the management of congenital pyloric stenosis to the pædiatrician. Only the occasional case which proves resistant to the "eumydrin" group of drugs now finds its way to the surgeon for a Rammstedt operation.

Malmö, which is a busy commercial town and seaport on the south-west coast, boasts of a large straggling general hospital, and is the main teaching centre for the old university town of Lund, only a few miles away. It looks across the narrow sound to Copenhagen, and has no doubt as many cultural contacts with Denmark as with the much more remote Swedish capital. An admirable institution here is the weekly pathological demonstration, when all the sections from the surgical department are projected on the screen and demonstrated by the senior pathologist. Professor Wulff is primarily a thoracic surgeon, and here again he has the enthusiastic support of a team of clinical workers. The management of the symptomless lung shadow picked up on mass radiography is a difficult problem for the thoracic surgeon. I met with it in every chest unit I visited. The risk of the morbidity and even mortality which may follow a thoracotomy is unjustified, if curiosity alone is the excuse for operation, but the chance of being able to remove a simple growth before it has caused disabling complications, or even of resecting a very early malignant tumour, is one not lightly to be missed. Some interesting work is being done here on the severe secondary anæmia which so often follows the surgical treatment of cardiospasm, a complication which has also received some attention in this country.

One can best judge the real quality of a country's surgical practice by its excellence, or otherwise, in hospitals far removed from the major teaching centres.

I made the trip to Örebro, a busy community of 70,000 or so, about 100 miles to the west of Stockholm because I had heard of its very active hospital and its energetic and far-seeing senior surgeon and director. As an index of the real worth of Professor Bohmansson, it is sufficient to say that a junior job with him is much sought after, and he numbers his former assistants among many of the most distinguished surgeons



in the land. His hospital is a model of contented efficiency. He is a surgeon of very wide experience who has so obviously never ceased to think and to learn. It was he who headed the team which investigated the use of "Dextran" and the early clinical trials were made in his surgical charge. It is now used very generally in Sweden, to the almost complete exclusion of plasma. Earlier troubles in the evolution of the optimum molecular size seem now to have been resolved, and it is given in liberal amounts with little fear of any undesirable reaction. I was somewhat surprised to find that even in Sweden it is still expensive, and for this reason I believe that it has not found general favour in Denmark.

Although I had no opportunity to visit Bauer in Mariestad, I was a little disappointed to find less talk of thrombo-embolism and of heparin than I had expected. Great emphasis is placed everywhere on early rising, and it was Bohmansson who devised the wheel chair which he later described in the *Lancet* in "Revolt from the Bedpan." \* Whereas in Crafoord's clinic resort to the heroics of the Trendelenburg operation was in former times by no means uncommon, the tray which stands at all times ready, has for long remained quite undisturbed. I enjoyed the story of a Swedish surgeon of some eminence who had a peripheral arterial embolectomy done by Einar Key himself, but with a somewhat disappointing result. He was in consequence reluctant subsequently to operate on any case of arterial embolism and contented himself if possible (and this was certainly true in the popliteal fossa) to massage energetically over the site of impaction in the earnest hope that he might fragment the clot and allow it to pass distally to a level where occlusion of the vessel would be of little consequence. It is interesting to note similar success by this manoeuvre recently reported by Piercy in the management of periphereal embolism in thyrotoxic disease.

In Karlskoga, a relatively small industrial community made famous by the Bofors armament factory, is a very new general hospital of 200 beds. Situated on a glorious site on the lakeside it has every facility to offer the enterprising general surgeon. How contentedly our younger surgeons could work and learn in such an environment.

Denmark, like our own native land, bears still many of the marks of the war years, and there is less in evidence in the hospitals of the things new and expensive, everywhere so evident in Sweden. But the Danes are a lively and a vigorous people and like all thoughtful surgeons everywhere they are still busy looking for the right answer to the common surgical problems—the management of the malignant breast which holds out most promise of long survival: the indications and limitations of surgery for the young man with a recalcitrant high acid ulcer.

Stimulated no doubt by the work of Aalkjaer in Aarhus, a great deal of attention is being paid to the careful control of the water and

\* *Lancet* (1947), 2, 509.

salt balance both before and after operation, but I found it no easier here than I do at home, to know when to disregard the day-to-day values of blood and urinary chlorides, alkali reserve, hæmatocrit and the rest and to follow only the older indices in the skin, the face and the tongue.

The traditional general surgical charge promises to disappear, as *orthopædics*, *proctology*, and the like tend to become marked off as the peculiar province of the "specialist." It has long been argued (and nowhere so persistently as in my own Edinburgh school) that only the mixed surgical ward, where fractures and burns, appendicitis and the enlarged prostate, empyema and hallux valgus, lie side by side, can serve as the proper training ground, if not for all young surgeons, certainly for the undergraduates. It is true that the increasing complexities and refinements of modern surgical methods, make it more than ever important that we should insist at all costs on presenting a balanced and general review of the whole subject, but there can, I believe, be no question that only by some measure of segregation and study of selected disease can a surgeon acquire the wide experience which makes his teaching for the post-graduate thoroughly convincing. But in Scandinavia, not only are big centres of population few and far between, but many of the young surgeons go out to work in the small hospitals in the country where they must of necessity be able to turn their hand to almost anything: it is no doubt for these two reasons, both right and natural, that narrow specialisation is, so far, in Scandinavia, less frequent than it is in Britain, or, of course, in the United States.

In Denmark as in Sweden, I was interested in the training of the surgeon in his early years. There is much to be said for the prolonged apprenticeship punctuated by the preparation of an exhaustive thesis for a *doctoreate*. There can be no question that this may be a most valuable interlude in a surgical career. However, from my short contact with junior surgeons both in Sweden and Denmark, I must reluctantly admit that the period of intensive study ranging over the whole field of surgery, which preparation for our higher surgical degrees increasingly demands, can prove of the greatest value to a surgeon in later years. But too often the passing of the Fellowship is accepted as the hall-mark of surgical maturity, and with his diploma safely tucked under his arm, the young surgeon hurries forth, diligently to operate, forgetful too often that it is only now that he can really begin to learn. He is no longer content to linger in his teaching school where opportunities to undertake major surgery are somewhat limited and tend to be the privilege of the selected few. Let him work, let him operate, but only under supervision, insisting always on a high quality of performance, inviting criticism and enquiry and perhaps most important of all, giving him the time, the place and the encouragement to do original work. When I think of Örebro hospital and of its enthusiastic director, of its excellent facilities for abundance of work

under ideal conditions, it becomes obvious that the stimulating environment is no monopoly of the teaching hospital. We tend in this country to have two types of hospital. First there are the teaching centres where competition for work is fierce and where wide experience and training is generally available only to the selected surgeons who are already earmarked for staff appointments : and secondly the very busy provincial hospitals with a part-time consulting staff where a large share of the major surgery may be early entrusted to an inexperienced registrar. It would help materially in the training of surgeons if we could develop hospitals of 300 or 400 beds on the Swedish model (or like that in the old Danish cathedral town of Roskilde) where continued training for the young surgeon would be the rule with abundant opportunity for practical experience, but only under the watchful eye of critical senior colleagues. But this would not be enough. He would require an energetic and capable pathologist and an equally enterprising radiologist, with, of course, a physician to match. For team work in a single unit and the closest co-operation with other departments stimulates discussion and furthers knowledge.

If a state medical service has given Scandinavia the admirable facilities for contented service which our surgical colleagues seem so commonly to enjoy, and more important still the luxury of having time to stop and think, it has indeed done well.

I wish I thought that it will do the same for us nearer home.

# ACUTE ISCHÆMIA OF THE LOWER LIMB AS A COMPLICATION OF TRANSFUSION WITH PLASMA

By HUGH A. F. DUDLEY, M.B., Ch.B.

SERIOUS local accidents associated with intravenous therapy are fortunately uncommon. The following case is of interest in view of this rarity and of the unusual nature of its pathology.

## CASE HISTORY

A healthy male child, aged 20 months, was admitted to the Burns Unit of the Royal Hospital for Sick Children three hours after sustaining a 40 per cent. body surface scald involving head, neck, upper limbs and trunk. He was in a state of severe shock; a plasma transfusion was started at once by cutting down on the right internal saphenous vein, 4 cm. above the medial malleolus. No difficulty was encountered and in spite of the known high incidence of spasm in the leg veins when used for transfusion (Gibson and Brown, 1945), the drip ran at the required rate until discontinued 22 hours later. No positive pressure was applied at any time. The child's clinical condition, blood pressure and hæmoglobin were satisfactorily maintained during the initial stages which included the application of pressure dressings without any extensive cleansing of the scalded areas. He gave no unusual cause for anxiety during his first twenty hours in hospital, though he did demonstrate the not uncommon hypertension of burnt children in addition to marked oliguria. Twenty-three hours following the injury he was noted to be not quite so well—restless and of poor colour, in spite of satisfactory blood pressure; the transfusion was running well, an adequate replacement had been given (1.5 litres, approximately), and the only positive finding was coldness of the right foot. No significance was attached to this though it was routinely noted that both the dorsalis pedis and posterior tibial pulses were present. The transfusion was accordingly continued. At this time and subsequently there was no evidence that there was or had been any postural factor or constrictive agent interfering with circulation in the limb. One hour later, coincident with a slight fall in blood pressure and a further deterioration in his general condition, a dramatic change was observed in the lower leg and foot. The capillary circulation had become very sluggish, a cyanotic colour had developed and arterial pulsation in the foot was absent. The popliteal pulse could not be felt in either leg but both femoral pulses were present. The drip, which was still running, was transferred immediately to the other leg, but in spite of this the child continued to deteriorate and died three hours later. Death appeared to be due to persistent shock from the original

injury, aggravated by the vascular accident in the leg. During the three hours preceding death the clinical appearances were those of an acute ischæmic process of very rapid progression. The skin became blotchy purple, almost violet in colour, quite cold and anæsthetic, the capillary circulation completely absent and the calf muscles tightly contracted, producing plantar flexion of the foot and clawing of the toes. The process was sharply delineated just above the middle of the calf by an almost horizontal line, proximal to which the skin was normal.

A dissection of the leg was carried out two to three hours after death. There was no difference in the girth of the two calves but moderate tension existed deep to the fascial layers below the knee, the calf muscles bulging out and appearing pale and œdematous when the coverings were incised. The main vascular tree was traced from the aortic bifurcation. The veins were uniformly slightly distended but contained either fluid blood or recent post-mortem clot; there was no evidence of massive venous thrombosis having occurred before death. The saphenous vein was rather more distended than the rest but it and the site of cannulation were healthy. The iliac, femoral and popliteal arteries were normally distributed, healthy and contained a little blood. In the distal part of the right popliteal artery and throughout the whole arterial tree beyond, there was apparent intense spasm, the vessels being cordlike and empty; no definite point of commencement could be found and there was no thrombus at any level. This spastic appearance was the only evidence of obstruction found. Microscopic sections of skin, muscle and the main vessels above and below the knee showed nothing grossly abnormal: death had occurred before any noteworthy changes could have had time to occur. In particular there appeared to be no damage to the arterial wall in the several sections examined.

The autopsy was completed 24 hours later, the appearances being those of severe scalds and adding nothing of interest in the present connection.

### DISCUSSION

Acute ischæmia associated with definite intravenous transfusion is probably excessively rare though such events are not often reported. Two cases have been described (Martin and Bodian, cited by Cohen, 1948) following forced plasma transfusion in infants, but in these there was apparently definite intra-arterial thrombus. Infarction of muscle secondary to irritant venous thrombosis, with or without subsequent contracture, is also known, but in such cases the ætiology is clear. In the present case four possible mechanisms can be suggested to account for the observed acute ischæmia. These are: (1) massive venous thrombosis; (2) retrograde arterial obstruction through large arteriovenous anastomoses; (3) pressure occlusion of the blood supply; and (4) arterial spasm.

Of these, the first is a recognised spontaneous cause of acute ischæmia and gangrene in the lower limb: its development during transfusion has been mentioned and though initially thought to be the most likely cause of the present complication, it was eliminated by the post-mortem findings.

The second was advanced by Cohen to explain the cases of Martin and Bodian and certain other vascular phenomena associated with very rapid transfusion under positive pressure. The arteriovenous communications implicated, though known to exist, have not as yet been shown to be capable of carrying such a retrograde flow, and, as has been mentioned, such cases are associated with the presence of intra-arterial thrombus.

Severe pressure from outside the vessels may certainly impede or obstruct the circulation of a limb and the distension of fascial planes by plasma from a slipped cannula could possibly produce this. No evidence of this was found either ante- or post-mortem, and though there was some tension deep to the deep fascia, this was not sufficient to occlude the vessels and could be adequately accounted for by the direct effects of anoxia and ischæmic muscular paralysis (Medical Research Council, 1944).

There remains arterial spasm, a hypothesis which is supported to a limited extent by the post-mortem findings, though it must be emphasised that such appearances can be mimicked to a certain degree by agonal contraction of the vessels. The localisation of the spasm to the vessels below the distal part of the popliteal would, however, explain the distribution and the rapid development of the ischæmia as it is well recognised that this is the site of arterial obstruction especially prone to cause speedy devascularisation to the middle of the calf. The intense cyanosis quickly produced is also some slight support for an arterial lesion in view of the proof by Lewis (1934, 1936) that such an appearance is characteristic of arterial stasis and not of venous obstruction.

Arterial spasm is an uncommon cause of acute ischæmia, for, though it has been long established that a varying degree of spasm may be initiated by numerous circumstances and may accompany very mild arterial injury or no detectable injury at all, resolution is the rule before serious consequences have had time to develop. In most cases that progress to acute ischæmic damage of the limb there is also evident damage to the arterial wall—the result of open or closed injury in neighbouring structures—but, particularly in association with crush injury, there is sometimes found an apparently normal vessel. It is to this last group that the present instance bears some resemblance. Cohen (1944) has explained such occurrences on the basis of a "reflex" arising in the damaged interstitial tissues; it is possible to extend this concept to include the veins as a source of afferent impulses and so to cover the event occurring during a transfusion. The saphenous vein, either irritated by the rapid flow, or

perhaps, in view of its acutely angled termination and narrow deep communications, over-distended by plasma, might react by spasm which, if continued, could be a source of similar contraction in the arteries; the pathway of spread of the spastic process being either reflex or direct through the arteriovenous anastomoses. Further, the vessels would in the present case be in the state of hyper-irritability known to exist in shock and would react to any stimulus in an exaggerated manner. The saphenous vein may go into spasm—often intense and painful—as a response to distension by pressure or to the insertion of a cannula, and in fact there are few who have not experienced difficulty from this source in getting a transfusion to run just when it was most needed. There is, of course, no evidence that such a spasm could either spread to the arterial side of the circulation, or act as an irritative focus for afferent stimuli which would set up the contraction of the arteries reflexly.

The case described constitutes a rare hazard of transfusion. It is well, however, that it should be borne in mind as a possible local complication of intravenous therapy.

## NEW BOOKS

*Tuberculosis of the Knee Joint.* By J. MORTENS. Pp. x+550. London: H. K. Lewis. 1948.

We regret that when the review of this book appeared on page 373 of Volume LVI. the price was wrongly stated. It is sold for 37s. 6d. net.

*The National Health Service.* By CHARLES HILL and JOHN WOODCOCK. Pp. x+283+cl. London: Christopher Johnson. 1949. Price 16s. net.

Dr Hill and Mr Woodcock have rendered a most useful service to all, doctors, dentists, chemists and laymen alike, who have to do with the National Health Service. The book might be entitled "The National Health Service Acts Explained," for that is what the authors have successfully attempted to do. It would be wrong to suppose, and the authors do not claim this, that the Acts have been explained and made easy for the mass of detail in the Acts and Regulations is confusing even to those who have studied them. Here, however, are the provisions of the Acts set out in simple language with explanatory comment where necessary. Five chapters are devoted to the Hospital and Specialist Services, eight to the General Medical Services, six to other Services, including a most useful chapter on Superannuation. In fourteen Appendices covering 111 pages there is set out a great deal of factual information ranging from the names and addresses of clerks of executive councils to the regulations governing pay-bed accommodation. The index is very complete. The print is clear and the volume of convenient size. It can be confidently recommended to Health Service workers of all categories.

*Sir William Gowers, 1845-1915.* By MACDONALD CRITCHLEY, M.D., F.R.C.P. Pp. 118. London: William Heinemann (Medical Books) Ltd. 1949. Price 17s. 6d.

Neurologists everywhere owe Dr Macdonald Critchley a great debt of gratitude for his painstaking and exceedingly attractive biography. To him has fallen the onerous task of showing those who follow what sort of man this was, whose example of industry, accurate observation and sheer competence, have inspired not only his own disciples but the next generation in turn. His published work, which is here carefully listed, was stupendous by any standard.

Everyone interested in disease of the nervous system should study this model pattern of not so very many years ago. Dr Critchley has executed his task uncommonly well.

*Skin Diseases in General Practice.* By F. RAY BETTLEY, T.D., M.D., F.R.C.P. Pp. 256, with 96 illustrations. London: Eyre & Spottiswoode (Publishers) Ltd. 1949. Price 21s. net.

The author has found that over 80 per cent. of dermatological cases fall into some ten common diagnoses. His aim has been to present the practical problems involved in the diagnosis and treatment of those common disorders. With commendable courage he has refrained from even brief mention of the others.

The young general practitioner whose knowledge of dermatology is often not of a practical type and who finds that approximately 7 per cent. of his patients have dermatological complaints will find this book of inestimable value. The sections on treatment are especially helpful. The illustrations are unfortunately not in colour but the price is correspondingly low.



*Coronary Artery Disease.* By E. P. BOAS, M.D., and N. F. BOAS, M.D. Pp. vi+399, with 88 illustrations. Chicago: The Year Book Publishers Inc. 1949. Price 33s. net.

Although disease of the coronary arteries has existed for generations it is only in the past thirty-five years that our knowledge of this serious condition has been clarified. The authors have attempted to correlate the normal vascular pattern of the coronary arteries with the development of atherosclerosis and the resulting clinical features. The investigation, differential diagnosis and treatment of these cases are discussed at length. The bibliography contains over 400 references and is an important contribution to the literature about a subject which has assumed a serious significance in the causes of disability and death of the population of to-day.

*The Sulphonamides in General Practice.* By EDWARD D. HOARE, M.D. Pp. 90. London: Staples Press Ltd. 1949. Price 5s.

This small book describes the indications for sulphonamide therapy and gives practical guidance as to the choice of drug and dosage. The possible toxic manifestations are described and the relationship of penicillin to sulphonamide therapy is discussed. As a practical guide this book could not be bettered and it can be thoroughly recommended.

*A Companion in Surgical Studies.* By IAN AIRD, CH.M., F.R.C.S. Pp. viii+1060. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 63s. net.

At long last this remarkable book has arrived. Large numbers of post-graduates in Edinburgh have been waiting keenly for its appearance, which has been delayed in printing for over two years. This book is the "end product" of the lecture notes which the author used in his post-graduate classes before the war. It is a veritable encyclopædia of information and covers the whole field of surgery except plastic work and orthopædic surgery. Each subject is dealt with in detail, including previous and present opinions which are given together with a most adequate list of references. For preparation for examinations there can be few, if any, books more helpful than this. It has the great advantage of including useful information on many of the rarer conditions—matters which can never be found in the average book and which are so important to the examinee. Professor Aird is to be congratulated on producing a work so detailed and comprehensive, which yet covers such a vast field.

*A History of Oto-laryngology.* By R. SCOTT STEVENSON, M.D., F.R.C.S.ED., and DOUGLAS GUTHRIE, M.D., F.R.C.S.ED. Pp. 155, illustrated. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 17s. 6d. net.

The authors point out that this is the first history of the specialty of oto-laryngology to be written. The completion of such a history entails a great amount of reading and also discrimination in which the authors have been thoroughly successful.

The earliest reference goes back to Egypt in 3500 B.C., from which it appears that rhinology is the most ancient of the medical specialties. The volume includes chapters on ancient history, the middle ages and Renaissance, seventeenth and eighteenth centuries, the nineteenth century when otology became a science, and modern history.

It is interesting to learn that Curtis, who founded what became the Royal Ear Hospital in London was a quack; and to be reminded that Garcia, the "father of laryngology" was a singing teacher. Many Scotsmen find honourable mention among the foremost oto-laryngologists of the late nineteenth and early twentieth centuries, many of whom will be known in person by readers.

Though a small volume, it successfully avoids being a mere catalogue. On the contrary, it is most readable and should give enjoyment to all who are interested in medical history, while being of particular interest to ear, nose and throat surgeons.

*Clinical Aspects and Treatment of Surgical Infections.* By FRANK L. MELENEY. Pp. 840, with 287 illustrations. London: W. B. Saunders Company. 1949. Price 60s.

Both surgeons and bacteriologists will welcome this monograph by Dr Frank Meleney whose pre-eminent authority to write such a review is unlikely to be questioned. It is a companion volume to his *Treatise on Surgical Infections* which dealt with the more fundamental problems, while this volume reviews the various "surgical infections" for the most part on the basis of an anatomical grouping. A full account is presented of the pathogenesis, pathology, bacteriology, clinical features and treatment of each. Publication of the work was postponed until an accurate appraisal of the value of chemotherapy and the modern antibiotics could be made, and this very valuable feature pervades every line on treatment and is no mere afterthought or footnote. The book can be recommended as a mine of interest and information.

*An Account of the Schools of Surgery: Royal College of Surgeons, Dublin, 1789-1948.* By J. D. H. WIDDESS. Pp. 107, with 16 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 17s. 6d.

In 1789, the Dublin surgeons put into practice the resolve embodied in their first charter, "to establish a liberal and extensive system of surgical education in our said Kingdom." Although concerned chiefly with the education of surgeons, they sought to provide a sound training for the general practitioner by uniting surgery, medicine and midwifery, in spite of the fact that such training did not become compulsory until 1886, when an amendment to the Medical Act of 1858 was passed. The Royal College of Surgeons in Ireland has a long history, dating as it does from 1446. In that year the Guild of St Mary Magdalene, to which the Dublin barber-surgeons belonged, was incorporated by Henry VI. It may thus claim to be the first medical corporation in Great Britain to obtain a Royal Charter. The greater part of the present story, however, is concerned with the eighteenth and nineteenth centuries. The College held its first meeting in 1784, under the Presidency of Samuel Croker-King, and proceeded forthwith to set up a system of surgical and medical education. The steady advance since that day, and the work of some of those who were trained in the School—Abraham Colles, Robert Adams, Robert William Smith, Alexander Macalister and others—are well described in this little book of just over a hundred pages, by the Librarian of the College. It is elegantly produced, the paper and printing are excellent, the illustrations consist of 16 plates, and there is a list of professors, a bibliography and an index.

*Care of the Surgical Patient.* By JACOB FINE, M.D. Pp. 544. London: W. B. Saunders Company. Price 40s.

This is a somewhat unusual book. It is not intended to be a textbook of surgery. The author expects that it will serve "as a ready guide for the over all care of the surgical patient." It is written in an easy, informal manner and yet covers a large field of medicine. There are chapters on diabetes, skin disorders, pediatrics and even the treatment of common acute poisoning. This is a fault. It is doubtful if this book will be a help to the doctor for it is lacking in detail. Indeed it is not unlike a popular encyclopædia in that all the subjects are presented as headings, but thereafter given only the barest outline. Thus cardiac disease and breast are each completed in three pages. The most useful part of the book is undoubtedly the section on clinical and laboratory methods in which details are given of the procedures. Because of the friendly style in which it is written and because it lacks the burden of detail, it makes very pleasant, if somewhat unprofitable, reading.

*Diagnostic Tests for Infants and Children.* By H. BEHRENDT, M.D. Pp. xvii+529. with 45 illustrations and 76 tables. London: Interscience Publishers Ltd. 1949. Price 45s. net.

This comprehensive book of reference on the principles, practice and interpretation of clinical and laboratory procedures in infancy and childhood will rapidly become an indispensable volume on the shelves of all engaged in pædiatric practice. It is a great convenience to have, for the first time, all the technical information of current value in pædiatrics collected together in one volume. It is written for a wide range of readers—the practitioner in a hurry for specific data, the clinician desiring detailed information for the investigation of a given problem, and the laboratory worker in search of technical data for immediate practical application. In attempting to meet such diversified needs, the author's main objective has been to bring out as clearly as possible the special considerations and technical data made necessary by the physiological peculiarities of the growing child; he has included all physiological functions which it may be desirable to test in children, even psychological testing, but he has omitted investigations of a morphological nature such as routine procedures of urine, blood and stool examination.

This book is the answer to the harassed worker's prayer for easier accessibility of all relevant technical knowledge.

*The Story of the Johns Hopkins.* By BERTRAM M. BERNHEIM. Pp. 274, illustrated. Surrey: World's Work Ltd. 1949. Price 12s. 6d.

The two American Medical Institutions best known on this side of the Atlantic are the Mayo Clinic and the Johns Hopkins Hospital. The foundation of a university and medical school at Baltimore by the morose Quaker bachelor, Johns Hopkins, who succeeded to his uncle's wholesale grocery business and made a fortune, is a truly astonishing tale, especially as Hopkins himself was neither student nor traveller, but simply a shrewd and determined man of affairs. There can be little doubt that the dramatic success of the medical side of Johns Hopkins University was the work of the four great doctors who appear in Sargent's masterly painting—Welch, Osler, Halsted and Kelly. Daniel Gilman and John Shaw Billings planned the new institution between them in 1876. Welch, the pathologist, came in 1885, and he brought Halsted, the surgeon, in 1889. Welch became a leader in bacteriology and public health, and in his later years he created the Institute of History of Medicine. Halsted, the great surgical technician, originator of rubber gloves and of much else, was joined by Finney. Osler, the physician, was perhaps the greatest of the four, and the quartette was completed by the gynæcologist, Kelly. How the four worked together in the celebrated Hopkins team, and how their work was developed and increased in surgery by Cushing, in urology by Young, in obstetrics by Whitridge Williams, and by others scarcely less eminent, forms a fascinating story which is well told in this book by a former member of the surgical staff. It is a work which deserves the attention of all who are interested in medical education.

*Bedside Diagnosis.* By CHARLES MACKAY SEWARD, M.D., F.R.C.P.ED. Pp. xii+372. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 17s. 6d. net.

In this small book Dr Seward discusses most of the common presenting symptoms of disease. The normal anatomical and physiological mechanisms of the body are enumerated, and the many derangements affecting these normal processes and their resulting symptoms and signs are discussed at length. The further investigations which may help to establish the diagnosis are described clearly and concisely.

This book presents the rational approach to the investigation of disease and exemplifies the method of sound diagnosis. It can be thoroughly recommended to all physicians.

*Varicose Veins.* By R. ROWDEN FOOTE. Pp. xiv+225, with 181 illustrations. London: Butterworth & Co. (Publishers) Ltd. 1949. Price 32s. 6d. net.

Despite the fact that varicose veins cause much suffering and views on treatment are at variance, no volume devoted entirely to this important subject has previously been published in Great Britain. Rowden Foote has, therefore, filled an important gap with his publication. The author, whose experience in this branch of surgery is unrivalled, has produced a volume which surgeon, general practitioner and post-graduate student will find a useful addition to his library. The anatomy, physiology and pathology are fully considered and the controversial subject of treatment is discussed in great detail. The advantages and disadvantages of the commoner sclerosants and the operative procedures are presented in unbiased fashion. A suitable scheme of treatment for the various types of varicosity is suggested, a scheme which will find few antagonists. The complications of varicose veins are also discussed. Interesting notes on the historical landmarks in the treatment of varicose veins are included.

*Discoveries for Medicine.* By WILLIAM H. WOGLOM. Pp. 229. London: Oxford University Press. 1949. Price 18s.

Throughout its long centuries of progress, medicine has owed much to the allied sciences; to chemistry, to physics, to biology and to the branches, now so numerous, of each of these sciences. Discoveries which have advanced medical learning have not always been the work of those engaged in practice. Some of the most noteworthy discoveries have been made by men outside the ranks of the profession, such as Garcia, the singing master, who contrived to see his own vocal cords and thus, unintentionally, founded the specialty of laryngology; Pasteur, the chemist, who gave Lister the idea which was to revolutionise surgery; Stephen Hales, the curate, whose enquiring mind led him to investigate the flow of sap in plants, and the blood pressure in animals; Benjamin Jesty, the farmer, who, as the writer correctly states, anticipated by twenty-two years Jenner's discovery of vaccination; Röntgen, the physicist, who by a happy chance, discovered X-rays; and "the old woman in Shropshire," of unknown name, from whom Dr Withering received the recipe for dropsy, and so discovered digitalis. These and other persons have been selected by the author for his work so aptly entitled, *Discoveries for Medicine*. It is fair and proper that medicine should acknowledge the debt to those, who, though not of the profession, have brought credit to it. There are eighteen chapters, ranging from respiration to heredity and from spectacles to phagocytosis. This volume of interesting essays forms an excellent introduction to that fascinating field of study, the history of medicine.

## NEW EDITIONS

*Diseases of Women.* By Ten Teachers under the direction of CLIFFORD WHITE, M.D., B.S. LOND., F.R.C.P. LOND., F.R.C.S. ENG., F.R.C.O.G. Eighth Edition. Pp. viii+461, with 170 illustrations. London: Edward Arnold & Co. 1949. Price 25s.

The eighth edition of this well-known textbook written by ten London gynaecologists has been thoroughly revised and gives in a clear and readable way a very concise presentation of modern practice and opinion. Every care has been taken to overcome the difficulties of collective authorship by close collaboration at all stages of composition, so that the volume is well-knit together.

The chapter on the physiological action of the endocrine glands has been rewritten and gives a summary of the present position of that complex subject. In it is included a brief account of the diseases associated with pituitary, thyroid and adrenal dysfunction as these are of importance in gynaecological differential diagnosis. Here, as elsewhere in this textbook, opinion and fact are fairly distinguished.

The volume is essentially practical and clinical and can be confidently recommended to students and general practitioners.

*Handbook of Surgery.* By ERIC C. MEKIE, M.B., CH.B., F.R.C.S.E., F.I.C.S., and IAN MACKENZIE, M.B.E., M.B., CH.B., F.R.C.S.E. Second Edition. Pp. xvi+764, with 29 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 20s. net.

This concise handbook of Surgery is intended for last minute revision by the final year student who, having studied a larger textbook, wishes to refresh his memory on the more important features. This purpose is admirably fulfilled.

A wide field is covered, and the subject matter is up to date, and well presented.

Some of the sections deserve special mention. In the treatment of acute inflammation a good account is given of the use of the Sulphonamides, the treatment of their toxic effects, and Penicillin therapy.

In the chapter dealing with the general effects of injury a good description is given of shock, crush syndrome, and water and salt requirements.

The various types of intestinal obstruction are well described.

*Practical Orthoptics in the Treatment of Squint.* By T. KEITH LYLE, M.D., M.CHIR., F.R.C.S., and SYLVIA JACKSON, S.R.N., D.B.O. Third Edition. Pp. xii+271, with 151 illustrations including 3 coloured plates. London: H. K. Lewis & Co. Ltd. 1949. Price 35s. net.

This new edition has been brought up to date with much new matter gained from hospital experience and the particular ocular problems which arose in relation to flying during the war. The greater part of the book is given over to consideration of the squinting child, but the subjects of latent and paralytic squint are also fully and lucidly dealt with. With the co-ordination of the School Ophthalmic Service under the Hospital Service, the chapters on instruments and the layout and management of an Orthoptic Department will be helpful to hospitals creating an Orthoptic Department for the first time. The new edition will be of great assistance to ophthalmologists and will provide orthoptists in training with a sound basis on which to build their practical training.

*Recent Advances in Oto-Laryngology.* By R. SCOTT STEVENSON, M.D., F.R.C.S.ED. Second Edition. Pp. viii+395, with 106 illustrations and 8 plates. London: J. & A. Churchill. 1949. Price 24s. net.

This is an example of what Recent Advances should be. The text has been practically entirely re-written and much of the material of the previous edition has been discarded. The author has reviewed the extensive literature of recent years and is able to present his views on a wide range of subjects of topical interest. He aims at stimulating interest in problems of the ear, nose and throat and calls attention to recent advances in diagnosis and treatment.

This attractive and well-written book should appeal to the general practitioner and to those specially interested in this field of work.

*Surgical Technique and Principles of Operative Surgery.* By A. V. PARTIPILO, M.D., F.A.C.S. Fourth Edition. Pp. 676, with 997 illustrations. London: Henry Kimpton. 1949. Price 75s. net.

This monograph on surgical technique is largely written by the surgical staff of Loyola University Medical School.

The book is well laid out and the illustrations are clear and helpful. Of particular interest are the first six chapters in which suture and ligature technique is described in a detailed fashion not readily available in textbooks of this type.

The remaining chapters are devoted to the standard operations of abdominal, thoracic, vascular, plastic and thyroid surgery. The descriptions of the operations are classical and are therefore likely to be of more value to undergraduates and recent graduates than to practising surgeons to whom details of operative difficulties and complications are of greater interest.

In general, the book is written in a pleasant and readable style and can be recommended as a clear and well-illustrated exposition of standard surgical operations.

*Diseases of Children.* By Sir A. E. GARROD, F. E. BATTEN and H. THURSFIELD. Fourth Edition, edited by DONALD PATERSON, M.D., F.R.C.P., and ALAN MONCRIEFF, M.D., F.R.C.P. Vol. II, pp. vii+1033, with 380 illustrations. London: Edward Arnold & Co. 1949. Price 40s. net.

The eagerly anticipated second volume of the fourth edition of this famous British reference book is indeed welcome. The outstanding success of the first volume which was published last year will be amply emulated by its companion volume now published. The twenty-four contributors to this volume have presented the most comprehensive and up-to-date review of their respective subjects which is to be found in any British reference book on pædiatrics.

This volume contains eighteen sections. While all are excellent, the chapters on "Organic Diseases of the Nervous System," "Diseases of Bones and Joints," "Diseases of the Cardiovascular System," and "Infectious Diseases" are especially notable.

*A Textbook of Medicine for Nurses.* By E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P. Fifth Edition. Pp. xv+491, with 8 plates and 64 illustrations. London: Oxford University Press. 1949. Price 21s.

The important advances made in medicine and therapeutics during the past few years have necessitated an extensive revision of this well-known book. In particular the section on venereal diseases has had to be completely rewritten following the introduction of penicillin therapy. A new section on the neuroses has been included. The photographs and diagrams are clearly reproduced and well chosen to illustrate the text.

This volume should continue to prove a popular textbook for nurses preparing for their State examinations and for reference after qualification.

*Psychosomatic Medicine.* By EDWARD WEISS, M.D., and O. SPURGEON ENGLISH, M.D. Second Edition. Pp. xxx+803. London: W. B. Saunders Company. 1949. Price 47s. 6d. net.

The second edition of this book incorporates much new clinical material. This clinical material is concerned principally with how the psychiatric approach can be applied to the problems of general medicine. As one reads through it, it is obvious that there is an immense amount of carefully considered and stimulating information. There, however, is a certain critical lack and a tendency to accept the opinions of others—which are extensively quoted—without separating the wheat from the chaff. There is too great a tendency to link up diseases, such as arthritis and others, with particular personality types, and to base such opinions on the Rorschach test. To base clinical evaluations on more or less arbitrary tests is rather dangerous policy.

*Trends in Nursing History.* By ELIZABETH M. JAMIESON and MARY F. SEWALL. Third Edition. Pp. 632, with 111 illustrations. London: W. B. Saunders Company. 1949. Price 22s. 6d.

Some new material has been added and much rewritten by the two American authors in the third edition of their book which now surveys nursing events from earliest times to the present day. In its first section, the historical background associated with each succeeding phase of development is concisely and interestingly expressed. The later part covers the period following World Wars I and II and presents the events which lead to the understanding of the place occupied by nursing in the scheme of national social legislation and world affairs, but here, the International outlook tends to be obscured by the large proportion of this section devoted to American nursing and the ramifications of its professional organisations. This could only be of interest to the American nurse or the advanced student of nursing aff

*Textbook of Bacteriology* (Eleventh Edition of Muir and Ritchie's *Manual*). By C. H. BROWNING, M.D., LL.D., D.P.H., F.R.S., and T. J. MACKIE, C.B.E., M.D., LL.D., D.P.H. Pp. 907, with 226 illustrations. London: Oxford University Press. 1949. Price 50s.

The *Manual* has become modern—except in weight.

The new format provides a larger, more satisfactory page. The lay-out has been reconstructed, the subject matter brought up to date and the whole rewritten with few paragraphs in small type. Recent work has been included throughout in an unobtrusive fashion—mainly in connection with chemotherapy and coliform, protozoal and virus infections; the book therefore retains its original character. The references are complete for new information and are now compiled in alphabetical order under chapter headings; additional references are conveniently grouped under subject. Technical methods have been removed from the text and now form a separate section.

The text is not over illustrated but the micrographs and photographs of colonies in culture are excellent. A comparison of the micrographs selected from the last edition demonstrates the very high quality of the printing in this book.

The older nomenclature has been retained and generic and specific names appear in section headings.

Fungus infections are dealt with in masterly fashion, by the late Dr Cranston Low.

The book is larger, more factual and informative than the usual textbook of bacteriology; it will prove useful to students, post-graduates and bacteriologists.

*Materia Medica, Pharmacy, Pharmacology and Therapeutics*. By WILLIAM HALE-WHITE. Twenty-eighth Edition. Revised by A. H. DOUTHWAITE, M.D., F.R.C.P. Pp. viii+532. London: J. & A. Churchill Ltd. 1949. Price 16s.

Since the last edition of this popular textbook appeared two years ago the 1948 *British Pharmacopæia* has been published. All the changes in the new *British Pharmacopæia* have been incorporated in this revised edition which has been brought completely up to date. In spite of the many additions of new and important drugs the size of the book has actually been slightly reduced by the careful pruning of out-of-date remedies. This latest edition should further enhance the popularity of this standard textbook.

*Fractures and Dislocations*. By EDWIN O. GECKELER, M.D. Fourth Edition. Pp. xii+371, with 344 illustrations. London: Baillière, Tindall & Cox. 1949. Price 27s. 6d. net.

Students often complain that there is no good concise book on fractures, and they can be warmly recommended to study this work by a Philadelphia orthopædic surgeon. It is well designed for undergraduates and general practitioners, for it describes all the common fractures and dislocations briefly but not scrappily, and only the one most practical method of dealing with a condition is advised. The treatment is conservative, and there is little resort to internal fixation of fractures. The illustrations are profuse and excellent.

*The Business Side of General Practice*. By THEODORE WIPRUD. Second Edition. Pp. xi+232, illustrated. London: W. B. Saunders Company. 1949. Price 17s. 6d.

The author interprets medical "business" widely. Besides the expected articles on selection of practice, records and accounts he includes chapters on personal finance, writing for the medical press, public speaking and so on. However, as the problems are discussed in an American setting there is little of practical value to the practitioner on this side of the Atlantic.

*Illustration of Surgical Treatment, Instruments and Appliances.* By ERIC L. FARQUHARSON, M.D., F.R.C.S.ED., F.R.C.S.ENG. Third Edition. Pp. xii+391, with 383 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 25s. net.

The third edition of this book has been thoroughly revised and is well up to date. It is intended primarily for the student preparing for the final examination, and also for reference by the young house surgeon.

It deals principally with fractures and orthopædics, and the descriptions of the common procedure are clear and concise and stress the important practical details. The text is profusely illustrated with well-chosen diagrams and photographs, each one of which clearly demonstrates the intended lesson. There is a comprehensive and well-illustrated appendix which demonstrates clearly by diagram and text the common surgical instruments and their uses.

This is a useful practical book for the surgical aspirant.

*Oral and Dental Diagnosis.* By K. H. THOMA. Third Edition. Pp. 563, with 776 illustrations. London: W. B. Saunders Company. 1949. Price 47s. 6d.

Much of the text in the third edition of *Oral and Dental Diagnosis* has been rewritten and numerous illustrations have been added. The book covers diseases and abnormal conditions of the teeth, jaws and associated parts, as well as the principles of treatment. In addition to primary lesions, the secondary manifestations which are symptoms of general disturbances are carefully considered. The effects of oral infections on bodily health are also described.

The book is divided into two main sections. Part I deals with treatment planning and special methods of examination on a broad basis, while Part II describes the diagnosis of the various oral conditions and suggests methods of treatment. A bibliography is included but this would be more useful had it contained references to a greater number of British authors.

The book can be recommended to medical and dental students.

*The Foot.* By Professor F. WOOD JONES, D.S.C., M.B., B.S., F.R.S. Second Edition. Pp. vii+333, with 155 figures. London: Baillière, Tindall & Cox. 1949. Price 25s. net.

It is always a pleasure to read a book by Professor Wood Jones and this one is no exception. The foot and its functions is one of the mysteries of nature to most students of anatomy, and it is even more of a mystery after studying the usual anatomical textbooks. The author, however, with his easy and amusing writing, descriptive ability and obvious intimate knowledge and understanding has gone far towards elucidating the subject.

*A Practice of Orthopædic Surgery.* By T. P. McMURRAY. Third Edition. Pp. viii+444, with 191 illustrations. London: Edward Arnold & Co. 1949. Price 30s. net.

This book on orthopædic surgery is now in its third edition and many alterations and revisions have been made. The fundamental principles have not altered, but the many improvements in technique and methods of investigation have widened its scope and usefulness. The outstanding chapters are on the knee, the hip, and the back and McMurray clarifies his subject so that it is easy to follow for the young surgeon. In the book, however, one misses his dogmatic teaching and sometimes it is difficult to know which of the many methods he would choose.

This is an excellent book, beautifully illustrated and written, and no orthopædic surgeon, whatever his rank, should be without it.



## BOOKS RECEIVED

- BANKS, H. STANLEY, M.A., M.D.(GLAS.), F.R.C.P.(LOND.), D.P.H.(CANTAB).  
The Common Infectious Diseases (*Edward Arnold & Co., London*) 21s. net.
- Edited by BERENS, CONRAD, M.D., F.A.C.S. The Eye and its Diseases. Second  
Edition (*W. B. Saunders Company, London*) 80s.
- BURROWS, WILLIAM, PH.D. Jordan-Burrows Textbook of Bacteriology.  
Fifteenth Edition (*W. B. Saunders Company, London*) 45s.
- CANTAROW, ABRAHAM, M.D., and TRUMPER, MAX, PH.D. Clinical Bio-  
chemistry. Fourth Edition (*W. B. Saunders Company, London*) 40s.
- Edited by CHRISTOPHER, FREDERICK, B.S., M.D., F.A.C.S. A Textbook of  
Surgery. Fifth Edition (*W. B. Saunders Company, London*) 65s.
- By the late COMROE, BERNARD I., M.D. Edited by HOLLANDER, JOSEPH L.,  
M.D., and Collaborators. Arthritis and Allied Conditions. Fourth Edition.  
(*Henry Kimpton, London*) 80s. net.
- CUSTER, R. PHILIP, M.D. An Atlas of the Blood and Bone Marrow.  
(*W. B. Saunders Company, London*) 75s.
- CUTHRIE SMITH, OLIVE F., M.B.E., F.C.S.P.(HON.), T.M.G. Rehabilitation,  
Re-education and Remedial Exercises. Second Edition.  
(*Bailliere, Tindall & Cox, London*) 25s. net.
- Edited by FLEMING, Prof. Sir ALEXANDER, M.B., B.S., F.R.C.P., F.R.C.S.,  
F.R.S. Penicillin. Second Edition.  
(*Butterworth & Co. (Publishers) Ltd., London*) 30s. net.
- FRIEDBERG, CHARLES K., M.D. Diseases of the Heart.  
(*W. B. Saunders Company, London*) 57s. 6d.
- Edited by FULTON, JOHN F., M.D. A Textbook of Physiology. Sixteenth  
Edition (*W. B. Saunders Company, London*) 50s.
- GOLDBERGER, EMANUEL, B.S., M.D. Unipolar Lead Electrocardiography.  
Second Edition (*Henry Kimpton, London*) 52s. 6d. net.
- HALLIDAY, JAMES L. Mr Carlyle—My Patient.  
(*William Heinemann, London*) 15s. net.
- JOHLIN, J. M., PH.D., D.SC. Introduction to Physical Biochemistry. Second  
Edition (*Cassell & Co. Ltd., London*) 27s. 6d. net.
- JOHNSTONE, R. W., C.B.E., M.D., M.A., F.R.C.S.E., M.R.C.P.E., F.R.C.O.G., F.R.S.E.,  
and KELLAR, R. J., M.B.E., M.B., CH.B., F.R.C.S.E., F.R.C.P.E., F.R.C.O.G.  
A Textbook of Midwifery. Fourteenth Edition.  
(*A. & C. Black Ltd., London*) 30s. net.
- ORR, THOMAS G., M.D. Operations of General Surgery. Second Edition.  
(*W. B. Saunders Company, London*) 67s. 6d.
- PALMER, EDDY D., A.B., M.S., M.D. Stomach Disease as Diagnosed by  
GastroscoPy (*Henry Kimpton, London*) 42s. net.
- PICKLES, WILLIAM NORMAN, M.D.(LOND.). Epidemiology in Country Practice.  
(*John Wright & Sons Ltd., Bristol*) 10s. 6d.
- PRATT, GERALD H., M.D., F.A.C.S. Surgical Management of Vascular  
Diseases (*Henry Kimpton, London*) 70s. net.
- RAPER, KENNETH B., and THOM, CHARLES. A Manual of the Penicillia.  
(*Bailliere, Tindall & Cox, London*) 91s. 6d.
- ROMER, ALFRED SHERWOOD. The Vertebrate Body.  
(*W. B. Saunders Company, London*) 27s. 6d.
- SINGER, JACOB JESSE, M.D., F.A.C.P., F.C.C.P. Differential Diagnosis of Chest  
Diseases (*Henry Kimpton, London*) 52s. 6d. net.
- SKINNER, HENRY ALAN, M.B., F.R.C.S.(C.). The Origin of Medical Terms.  
(*Bailliere, Tindall & Cox, London*) 54s. net.
- SUNDERMAN, F. WILLIAM, M.D., PH.D., and BOERNER, FREDERICK, V.M.D.  
Normal Values in Clinical Medicine.  
(*W. B. Saunders Company, London*) 70s.
- TITUS, PAUL, M.D. Atlas of Obstetric Technic. Second Edition.  
(*Henry Kimpton, London*) 52s. 6d. net.
- Tuberculosis in the Commonwealth.  
(*National Assoc. for the Prevention of Tuberculosis*) 15s.
- WIGGERS, CARL J., M.D., D.SC., F.A.C.P. Physiology in Health and Disease.  
Fifth Edition (*Henry Kimpton, London*) 70s. net.

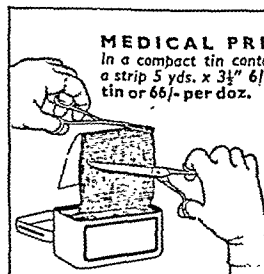
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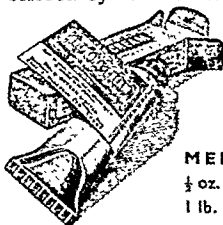
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# Edinburgh Medical Journal

*December 1949*

## THE SURGICAL MANAGEMENT OF THE MALIGNANT COLON

By MR G. T. MOWAT, F.R.C.S.E.

### HISTORY

THE history of modern colonic surgery, so far as is known, begins in 1832 when Reybard<sup>1</sup> excised a carcinoma of the sigmoid and did end-to-end suture, the patient dying of recurrence a year later. He was so roundly castigated for his temerity by his professional brethren that if he repeated the offence, it is not on record. A hundred years previously the prolonged European wars of the first half of the eighteenth century had stimulated the interest of military surgeons in intestinal suture and much was done. Linen and catgut sutures were used, being steeped in wines and spirits. Suture of bowel over a hollow cylinder was much in use, wood or animal trachea being employed. The use of these was followed at the beginning of the nineteenth century by the india-rubber tube. These were the forerunners of the Murphy and the Allingham Button so much in use at the turn of the present century. Thiersch in 1843 did an unsuccessful resection with anastomosis, but it was not until the advent of Listerian methods of antiseptics that colonic surgery began to be popular. In 1884 Billroth<sup>2</sup> reviewed 17 cases with a mortality of 60 per cent.—by 1890 48 cases had been published with a mortality of 45 per cent.

### EXTERIORISATION

When we consider the hazards of end-to-end anastomosis as experienced by the pioneers of colonic surgery and the high mortality which resulted, we cannot be surprised that fertile minds were seeking new methods of dealing with the problem. As is usual, different men in different countries hit on the same solution and exteriorisation was born. Schrede in 1879 was the first to exteriorise both bowel ends as he could not approximate them after resection, and in the same year Billroth, after resecting the pelvic colon, closed the distal end and took the proximal loop out as a colostomy. Thereafter, however, he continued his practice of primary anastomosis with high mortality.

A Honyman Gillespie Lecture delivered on 17th November 1949.

In 1891 Bloch,<sup>3</sup> of Copenhagen, published the first extrusion operation, and was followed by Paul,<sup>4</sup> of Liverpool, in 1895 and by Mikulcz<sup>5</sup> in 1902. Beginning as a simple extrusion of the pelvic colon with the tumour on its summit, and modified by Paul to removal of the extruded loop with a fairly wide mesenteric area and drainage of the proximal end by his well-known tube, the practice of exteriorisation extended until, in more modern times, after wide removal of colon and gland bearing area has been accomplished, decision has to be made whether to safely exteriorise or to risk primary anastomosis. The spur was destroyed at first by clamps, later by dissecting forceps and scissors, and later still by freeing the loop from the abdominal wall and restoring the continuity of the bowel by suture. Exteriorisation, by the end of the last century had reduced the mortality of resection of the colon to 15 per cent. and made surgery of the malignant colon possible, leading not only to bolder and wider resections but to a more intimate knowledge of pathology and spread.

Many of the disadvantages of exteriorisation are now past history. At an earlier period, insufficient removal of bowel and mesentery, recurrence at the site of extrusion, and difficulty in exteriorising widely separated loops were noted. For many years, however, its position has been that after wide resection of bowel and mesentery, the bowel ends are brought to the surface of the abdomen instead of being anastomosed, and these disadvantages have disappeared, the area resected being that of choice. *It was for long the safest method of renewing bowel continuity after resection and only in the past ten years have newer methods brought primary anastomosis to an equal or increased margin of safety.* Its real disadvantages are obvious—a discharging colostomy over a sometimes prolonged period, sepsis and following herniæ at the site of extrusion, and multiple procedures in a frequently old and debilitated patient—but it was reasonably safe, with an operation mortality varying from 17 per cent. in the time of Paul, to 10 per cent. and under, fifty years later. Its closure was often tedious—clamps for crushing the spur were, in the main, inefficient, protruding awkwardly from the abdomen, and only gripping the superior portion of the spur, the blades tending to diverge. A really efficient clamp has recently been made by Swanson, which lies snugly and grips equally along its length. Freeing of the exteriorised loops from the abdominal wall, with anastomosis and replacement of the sutured bowel in the abdominal cavity, is quicker and more simple. For this type of closure, however, no spur must be made at the time of exteriorisation, the loops being sutured together for a distance of only half an inch at as wide an angle as possible, and the loops drained. This has been my own method for many years and no leakage of fæces into the abdominal cavity has occurred, but stricture may appear at the site of anastomosis, usually five to seven years later, necessitating reanastomosis. If destruction of the spur by clamps is to follow exteriorisation a longer spur must be made. Vertical rotation of the

ends of the extruded bowel can be carried out before suture to prevent later crushing of the mesentery and to ensure easier obliteration of the spur. An advantage of exteriorisation in debilitated patients is its free external drainage of the proximal loop—there is no bowel distension, and, as a rule, an easy post-operative recovery from the resection. I have found drainage of the loops preferable to closure of the openings with clamps by the Rankin obstructive method.<sup>6</sup> Exteriorisation will still play some part in cases of obstruction where, after resection, the proximal loop is still found to be hypertrophied and inflamed, and where primary anastomosis is judged unsafe.

### ASEPTIC ANASTOMOSIS

In 1920 a new wave swept colonic surgery and for the next ten years aseptic or closed anastomosis became the dominant method in colon anastomosis. Based on the belief that infection of the abdominal cavity at the time of operation was responsible for the general peritonitis, the most ingenious methods, about fifty in all, were devised to prevent soiling of the abdomen during the anastomosis. All of these, however, had the same basis, the temporary closure of the cut ends of the colon by some occluding agent—clamp, ligature or suture—and suture of the bowel by Lembert's method over the closing agent, which was then removed. The cut edges for a varying distance were thus inverted into the lumen of the bowel in the form of a cuff, and peritoneal apposition was attained except at the bare mesenteric border. This area however, at the points most frequently resected, was narrow and could often be covered by adjacent peritoneum.

First suggested in 1908 by Parker and Kerr,<sup>7</sup> whose simple basting stitch method is still used, closed anastomosis is associated with the names of Seton Pringle,<sup>8</sup> Fraser and Dott,<sup>9</sup> Rankin and many others. The method favoured quick adhesion in that peritoneal surfaces were approximated, and vascularity in that, theoretically at least, the suture was seromuscular. In the hands of many surgeons it proved successful, and good results were obtained, the mortality at this period being in the region of 10-15 per cent. Mortality in less experienced hands, however, was much higher. It is significant that, after ten years of intensive use, closed anastomosis was replaced by a fresh wave of exteriorisation, although it retained some measure of support and is still the method of choice by some surgeons. In order to avoid the inversion of a long cuff into the lumen, clamps were narrow, holding the cut edge flush while anastomosing sutures were applied as near the clamp as possible, but necessarily at some distance from the cut edge, leaving some degree of inverted cuff, whose vitality was endangered not only by pressure with clamps, but by vascular damage owing to distant constriction by suture. Failure was generally due to gangrene, in whole or in part, of the inverted cuff, spreading to the suture line with late slough and leakage. Further, in a thin colonic

wall, seromuscular suture is often impossible, the needle perforating the lumen with leakage. A successful aseptic anastomosis in this type of colon requires a high degree of technical skill as well as a measure of good fortune, but, in the hands of surgeons with experience of this type of anastomosis, good results were, and still are, obtained. It is not, however, an operation for a beginner.

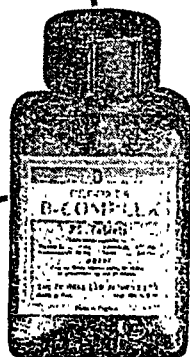
The ten-year period following 1930 was one of indecision and of stock-taking. It had become evident that the right half of the colon presented a completely different problem from that of the left, the latter being incomparably more difficult. It had long been recognised that a hemicolectomy and primary side-to-side or end-to-side anastomosis could, in the absence of obstruction, be done with reasonable safety on the right side, while a similar operation on the left was fraught with danger. The challenge of the left colon, however, was still unanswered and many surgeons had reverted to the exteriorisation method.

Writings and reports of this period are confused and conflicting. The hopes of safe immediate anastomosis by the aseptic method had not materialised—meticulous investigation into the blood supply of the colon in a search for optimum sites of section had not markedly decreased mortality. The most careful avoidance of Sudek's critical point, of the inclusion of parallel vessels in the cut edge, and the planning of colonic section with exposure of vessels to ensure efficient blood supply at the suture line, while decreasing the percentage of leakage, left an unsatisfactory percentage of failure. The variety of operative procedures in this period well illustrates the confusion of thought and practice of the time—hemicolectomy with preliminary proximal drainage, hemicolectomy with proximal drainage at the time of operation, short circuit drainage followed by excision a few weeks later, aseptic anastomosis, hemicolectomy followed by exteriorisation of various types, open, closed, protruding proximal loop, and many others. It was a period of varying success and failure but one in which the operability percentage was markedly raised, and when more radical operations in the presence of invasion by the growth of neighbouring organs had become common. Wider resections, too, of the lymphatic drainage were being carried out.

#### DEVINE'S DEFUNCTIONED COLON

The comparative success in excision of the right colon had for long been noted and minds were turning to the relatively low bacterial content of the ileum as an important factor in its attainment. Devine,<sup>10</sup> of Melbourne, was the first to translate this thought into action. Stating that the operation mortality for cancer of the colon varied in different clinics from 15-57 per cent., he published in 1935 his method of defunctioning and detoxicating the affected segment of the left colon, later doing a one-stage resection and anastomosis. The transverse

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colostomy through two separate openings to exclude any possibility of passage of faeces into the distal colon, and the cleansing and disinfecting of the excluded loop for several weeks by irrigation from both ends, reduced its infectivity and made anastomosis of the left colon safe. Its disadvantages were obvious—many operations—a long stay in hospital—and the leaving of a tumour *in situ* for a month or more before removal. Devine showed, however, that a left colon, when empty and detoxicated, could be resected and anastomosed with a safety hitherto unattained, anticipating, in some measure, modern pre-operative chemotherapy.

### OPEN ANASTOMOSIS

From this time onward, until chemotherapy was introduced, more and more attention was to be given to the vascularity of the cut edge of the bowel. Clamps close to the cut ends were being discarded and open anastomosis was becoming more popular, the peritoneal cavity being protected by gauze packs. Increased interest was being taken in the effect of sutures on the blood supply of the bowel, and interrupted sutures began to replace the continuous one. The danger of the tight continuous suture had been stressed by Grey Turner as far back as 1929 but the ever present fear of leakage had so far assured its popularity. In 1938 Wilkie,<sup>11</sup> who had contributed so much to this subject, further stressed that safety in colonic suture depended on maintaining the integrity of the blood supply to the cut edges rather than on immediate security against leakage. Two layers of interrupted sutures now became popular—the inner being carried through all coats, the outer being seromuscular. Not only so, but too close apposition of sutures was deprecated, the risk of devascularising the cut edge being rated higher than that of leakage. In the absence of obstruction, exteriorisation was being abandoned and colonic resection with primary anastomosis was given another trial. Results varied but those of experienced surgeons improved greatly. Between 1941 and 1943 Wagensteen and Toon<sup>12</sup> performed primary resection and anastomosis in 61 cases with one death. In the years 1943-45, with preliminary chemotherapy, 78 cases were operated on by them in a similar manner with 6 deaths. It will be seen, therefore, that bowel infectivity, although one of the major causes of gangrene and leakage, was not the sole one, and that strict attention to other factors, notably the blood supply of the cut edge, was, before the advent of intestinal chemotherapy, beginning to achieve the measure of success which had been so long striven for.

### CHEMOTHERAPY

Discovery of the sulphonamides introduced a new weapon into the surgical armoury. The criteria of an efficient colonic antiseptic are the competence of its action on colonic organisms, and its non-

absorbability from the intestinal tract, with localisation of action within the lumen. Poth *et al.*<sup>13</sup> in 1941, investigating the action of succinyl-sulphathiazole or sulfasuxidine, found that it satisfied both these criteria, only 5 per cent. of the ingested drug being excreted by the kidneys and its effect on the fæces being marked. In the investigation of 250 patients, within one to seven days of administration, the fæces became semi-solid, small in bulk, relatively odourless and the bacterial flora of the colon became considerably altered. The count of *Bacillus coli* dropped from an average of 10 million to less than one thousand organisms per gm. of wet stool. Of these 250 patients, 14 had resection and primary anastomosis of the left colon without death, the post-operative period being smooth. Poth<sup>14</sup> further found that the course of anastomosis, after sulfasuxidine premedication, differed materially from that in the untreated case. Diffuse peritoneal reaction, œdema, and easy disruption were absent, and healing was orderly and uncomplicated, when contrasted with the infection and delayed healing of the untreated colon. Sulphathaladine has the advantage of acting on anærobic as well as aerobic organisms and does not render the fæces so fluid and so liable to leakage. It is, however, antagonistic to penicillin, which in the post-operative phase, may be required for chest complications. Recent reports on the results of primary resection anastomosis, with preliminary chemotherapy, have been most encouraging. A report in process of publication by a member of my own unit, Barclay,<sup>15</sup> included 23 consecutive primary resection anastomoses of the left colon operated on by him within the past two years with no mortality. In this series, sulfasuxidine was used for preliminary chemotherapy—open anastomosis was used without clamps, the peritoneal cavity being protected by gauze packs, and the bowel united by end-to-end interrupted sutures of No. 0, twenty-day catgut, not too closely applied and not tied too tightly. The inner layer of sutures picked up the whole thickness of the bowel wall. The outer layer was seromuscular. One anastomosis was done well down in the extra-peritoneal part of the rectum and convalescence was uneventful. A mild degree of dilatation and hypertrophy was present in all cases, except one in which a preliminary cæcostomy had to be done in the presence of complete obstruction. In the first 14 patients alternate proximal drainage and complete closure were done in order to compare results, but when it was evident that all had an equally smooth recovery proximal drainage at the time of resection was abandoned. In doubtful cases, however, it does provide a measure of safety. The quietude of the post-operative period in these cases has been most impressive, none of the patients giving rise to any anxiety. The full action of chemotherapy still remains to be assessed, but its value is becoming evident, and, combined with a better appreciation of the preservation of the blood supply in the cut edge, gives promise of lowering the risk of primary anastomosis to that of an ordinary major abdominal operation.

## CAUSES OF FAILURE IN BOWEL ANASTOMOSIS

The mortality of primary anastomosis of the colon was due, in the large majority of cases, to general peritonitis and in a lesser degree to extra-abdominal complications, pulmonary, renal and cardiovascular. After three to ten days of normal recovery a greyish look in the patient's face, with a slight distension of the abdomen, ushered in a stage of rapid deterioration and death. Post mortem usually revealed a general peritonitis, a leak of varying size at the suture line often, but not always, at the mesenteric angle, and frequently accompanied by an area of gangrenous slough at the site of leakage. In the general disorder of general peritonitis it was never easy to reconstruct the series of events which led to the leakage. Experience of the past quarter century has crystallised our knowledge of the causes of failure of colonic anastomosis into three main channels :—

- (1) Difficulties in complete peritoneal approximation.
- (2) Vascular failure at the suture line.
- (3) The high infectivity of the colonic contents.

To those may be added a thin colonic wall, undue tension at the line of suture due to *inadequate mobilisation*, and the presence of appendices epiploicæ.

*Adequate Peritonealisation.*—The importance of complete peritoneal apposition around the anastomosis has long been recognised. In 1834 Travers, of Guy's Hospital, published his investigation into the healing of anastomosed intestine and stressed the rôle of the opposed peritoneum in promoting quick adhesion of the cut ends, preventing leakage and holding the bowel ends together while the more slowly uniting middle and inner coats consolidated. Lembert, sixty years later, confirmed Travers' findings and the Lembert suture, with its inverting apposition of peritoneum, played a large part in the advance of gastrointestinal surgery of his time. A more recent investigation has shown that while peritoneum adheres to peritoneum within twenty-four hours and in three days is firmly attached, anastomosis of a serous-covered segment of bowel to a segment devoid of peritoneum takes fourteen to twenty days to unite firmly. The danger of the uncovered mesenteric angle is obvious. The adhesion of peritoneal surfaces, therefore, at the site of anastomosis, affords, during the first five to six days, a period of safety within which the early processes of repair in the main coats of the bowel can establish themselves. Well peritonealised portions of bowel, should, as far as possible, be used for end-to-end anastomosis, the sigmoid, the transverse colon and the ileum being ideal segments. In these, bare areas occupy only about 5 per cent. or less of the bowel circumference and can be readily covered at the site of anastomosis by adjacent peritoneum. In the ascending colon less than 50 per cent. of the circumference is covered, making it unsuitable for this type of anastomosis.

Peritonealisation of the descending colon varies within wide limits from 50-90 per cent. and investigation should be made before deciding on its use. The presence of appendices epiploicæ in the immediate vicinity of the cut edge may make efficient approximation of peritoneum difficult. The terminal vessels encircling the bowel at right angles to the lumen send fine branches into the appendices and there is some danger of thrombosis if the appendices are removed and the vessels ligated. It is said also that the long terminal vessel may send a fine loop of its own length into the base of the appendix, and this may be ligated with the base. If the appendices interfere with peritoneal apposition, however, they should be gently removed as the danger of thrombosis is, in my own experience, slight, and peritoneal adhesion is an important factor in successful union. It may be possible to choose a site for bowel section with this in view.

*Vascularity of Cut Ends.*—The thinness of the colonic wall and consequent lack of protection to its blood vessels render the bowel liable to damage by clamp or sutures. The most difficult problem in end-to-end suture was, and is, that of suturing the ends firmly enough to prevent both hæmorrhage and leakage, but not so tightly as to produce vascular obliteration and gangrene. Undoubtedly many of the leakages were due to primary gangrene, produced by occlusion of blood supply by suture, and the delay in the onset of peritonitis, often of a week's duration, fits in with this picture. Thinness of the colonic wall may also make a seromuscular type of suture impossible without perforation, making inclusion of the whole bowel wall imperative, and interfering with blood supply from the sub-mucosal networks. Vascular causes of failure may lie either in the region of the anastomosis, or more centrally by interference with the main arterial supply to the segment of the bowel. Clamps too closely applied to the suture line are an obvious cause. The tight continuous suture in the presence of a thin atrophied bowel wall is another. In addition, thickening and narrowing of the colonic vessels as part of a generalised vascular disease will increase the risk of gangrene, even when neither clamps nor continuous sutures are employed. The colonic vessels break up near the bowel into a series of arcades from which smaller vessels divide into long and short terminal arteries, the antimesenteric border being supplied largely by the long terminal artery after it has partially encircled the bowel. Interrupted sutures give rise to less strangulation of the cut edge, and an oblique section, with removal of more of the antimesenteric region makes for safety. Section of the mesentery should be along natural lines of arterial supply, and before section a visual appreciation should be made that the loops to be anastomosed have a satisfactory blood supply. Resections will, naturally, fall between the distribution of the main colic arteries but these are apt to vary and a clear exposure of vessels is necessary.

*Infectivity.*—As has been shown the high infectivity of the contents of the colon makes healing of the anastomosis that of an infected

wound, with œdema, inflammation and delay in the reparative processes. The danger of cutting out of sutures and leakage under such conditions need not be stressed. With regard to soiling of the peritoneal cavity during operation, the peritoneum can take care of any slight soiling and it is doubtful if this factor has any great bearing on mortality.

### MORBIDITY

The measure of success in the surgical treatment of malignant disease rests on its late, no less than its early survival rate, and as put so aptly, if ironically, the question of "Can you sew two bowel ends together?" is less important than "Can you remove all of the cancer?" Approximately 40-70 per cent. of those patients successfully operated on have died within five years, the majority living less than three years. Survival rate is in inverse ratio to the operability rate, the criteria of which, among different surgeons, may differ widely. Wilkie, whose experience and skill in this branch of surgery ranks high, showed in his last series of cases a five year survival rate of 33½ per cent., but his operability rate is unsatisfactory. Death is, misleading, but at best late survival rate was high. Thus statistics can be apart from other causes, largely due to recurrences in the region of the anastomosis or to metastases in the lymphatic drainage with wide extension inside the abdomen. Operability has steadily advanced. Fixation of the tumour to neighbouring organs is being more radically dealt with, contra-indications to resection being peritoneal spread, secondary deposits in the liver and invasion of vital vascular channels, such as aorta or portal vein. Glandular enlargement should not contra-indicate resection as inflammatory involvement of glands from the ulcerated surface of the lumen is common. Frequently a presumed invasion proves to be merely adhesion and a stripping off can be successfully carried out. Most non-vital abdominal organs can be partially or wholly resected with the tumour. Tumours of the cæcum and ascending colon with late appearance of symptoms, frequently are found invading the abdominal wall, large portions of which can be removed with surprisingly easy closure. A more formidable problem is invasion of coils of small intestine, but after resection, the lie of the mesentery aids the necessary reconstruction of the loops in an iso-peristaltic direction.

### LYMPHATIC SPREAD

There was a tendency in the past to minimise the incidence of dissemination in colonic cancer both locally and in its lymphatic distribution. Tumours of the colon, however, vary widely in their grade of malignancy, and the more anaplastic tumour tends to quick local extension and to early lymphatic dissemination. In this type enlarged glands are usually evident, and the presence of a localised tumour with no apparent glandular enlargement should not preclude

wide resection with both local and lymph drainage eradication. Thorough investigation of the lymph drainage area has been made difficult and laborious by the high incidence of inflammatory enlargement of glands and the necessity for serial histological section of each individual gland to exclude small nodes of malignancy in the surrounding inflammation. These are easily missed, and the labour and time expended in a meticulous search for lymph metastases in any individual case can be very great. Craig and McCarthy<sup>16</sup> in 1923, found an incidence of glandular involvement in 100 colonic resections to be 37 per cent. In 1939 Simpson and Mayo<sup>17</sup> reported an incidence of 41 per cent. in 120 cases. As the Glasgow Royal Cancer Hospital, in some of my own cases, Woodhouse Price found a high incidence of microscopic malignant foci in otherwise inflammatory glands, occasionally in lymphatic areas adjacent to the normal lymph run. The brilliant and painstaking work of Gilchrist and David,<sup>18</sup> published in 1947 involving a labour of years, in a meticulous investigation of 200 resected cases of rectum and colon, showed a lymphatic involvement in 62 per cent. of cases. Using their modification of the Spalteholz method of clearing the tissues and visualising the lymphatic drain, they were able to make a more complete search than had hitherto been possible. Coller *et al.*<sup>19</sup> in 1941 had published similar results in the resected specimens of 46 cases of colonic cancer, using similar methods and finding that 60 per cent. showed evidence of regional lymph node metastases. It is interesting to note that in Coller's series the highest percentage—75 per cent. and over—was in the cæcum and transverse colon, the splenic flexure and descending colon having 66 per cent. In Gilchrist and David's series the right colon showed 86 per cent. lymph metastases, while 44 per cent. were present in transverse colon, splenic flexure and descending colon. The lowest five year survival rate, however, was in the latter group, being 37 per cent., suggesting that here lymphatic eradication tended to be incomplete. It seems clear, in view of these findings, that operative removal of the colon will have to include a more careful resection of the lymphatic drainage area than in the past has been considered necessary.

The classic work of Jamieson and Dobson<sup>20</sup> established our knowledge of the lymphatic drainage of the colon. The intramural lymphatic network in the intestinal wall itself drains into the extramural system of lymph vessels and glands which are grouped around the blood vessels and follow them centrally to their origins. The epicolic glands, situated on the colonic wall, and the paracolic glands, situated mesially but close to the bowel, present a simple surgical problem. More difficult is the problem of eradicating the chain of lymphatic drainage running centrally along the blood vessels towards the central group of glands surrounding the origin of the main artery, with the intermediate glands situated along the same path in the mesentery itself. Blockage of a normal drainage route by metastases or by inflammatory enlargement tends to spill the lymph flow into

adjacent lymph areas—or a tumour may be situated in one main drainage area corresponding to its blood supply, but so close to another that lymphatic metastases may be present in two areas. Selection of sites for resection will vary according to the site of the tumour but one must take into consideration not only removal of all mesentery up to and including the central group of glands, but any probable overflow into adjacent lymph areas. Areas of resection are largely determined by the direction of the main colonic arteries and clear cut regions between main arterial systems have been mapped out as safe areas for resection. The arterial arcades at the point of entry to the colon, however, provide a far from scanty blood supply and it is possible that danger of gangrene from lack of collateral circulation at the periphery between adjacent arterial areas has been, to some extent, overrated. If this proves to be so, more freedom in resection will result, and adjacent areas of lymph overflow can be dealt with more freely. It is, however, a cardinal rule that where the origin of a main vessel is ligated the corresponding segment of its distribution should be removed.

#### OPERATIVE PROCEDURES

*Right Colon, Cæcum, Ascending Colon and Hepatic Flexure.*—Tumours of the right colon are late in giving rise to symptoms and may attain a large size before discovery, the presence of a painless mass in the right side of the abdomen often being the first sign. The ileo colic group of lymph vessels drains the terminal ileum, cæcum and the greater part of the ascending colon, and the ileo colic central glands may extend as high as the duodenum and pancreas. Hemicolectomy will include the terminal 5-6 in. of the ileum and the proximal portion of the transverse colon with a mesial resection of the mesentery including the ileo colic and right colic groups of vessels up to their origins. Coller has shown, that, when the hepatic flexure is the seat of growth, in addition to the downward spread in the ileo colic channels, there is apt to be a mesial invasion of the middle colic region of drainage, which should be removed. This entails a wider resection of transverse colon with a large portion of omentum. The anastomosis of ileum to transverse colon may be end-to-end, end-to-side or side-to-side. It is important that in the last two methods no blind pouch should be left, as elongation and dilatation of this may occur to a surprising degree.

*Transverse Colon.*—The branches of the middle colic artery supply the proximal two-thirds of the transverse colon while the ascending branch of the left colic artery supplies the distal third. The lymphatics follow the same course. The lymphatic vessels of the transverse colon, however, communicate with those of the omentum, which may be invaded, with secondary involvement of the glands along the greater curvature of the stomach, in addition to both middle and left colic areas of drainage. Complete eradication will entail not only removal



of the middle and left colic drainage areas, but complete removal of the omentum with the gland bearing areas in the region of the pancreas and greater curvature of the stomach. This would involve section at points in the ascending colon and descending colon with difficult approximation, incomplete peritonealisation and unsatisfactory anastomosis. If the condition of the patient permits, a wider resection of the right colon with end-to-side anastomosis of the ileum to upper sigmoid makes for more satisfactory union. A more local excision is best suited to patients with a poor operative risk—the middle colic branches, should, however, be visualised and a good arterial supply to the bowel ends assured.

*Splenic Flexure and Descending Colon.*—An oblique incision gives good exposure. Tumours of the splenic flexure are often adherent but with care can usually be stripped from their surroundings. Lymph drainage of this region may overflow mesially into the middle colic area or downwards into the inferior mesenteric lymph group. The splenic lymph glands may be involved or dissemination may occur in the omentum. As wide a resection as possible should be done and in tumours of the descending colon should include the upper sigmoid loop and its drainage area as well as part of the transverse colon. Thorough mobilisation may be necessary for approximation without tension.

*Sigmoid.*—The inferior mesenteric chain of glands drains both sigmoid and rectum, the intermediate nodes which drain the sigmoid lying along the sigmoid vessels, while the central groups draining into the aortic glands lie around the origin of the inferior mesenteric vessels. The sigmoid drainage communicates above with the left colic area and below with the superior hæmorrhoidal. In lesions of the upper sigmoid intra-peritoneal operations can be done, with excision of the adjacent left colic and sigmoid regions, and eradication of the inferior mesenteric glandular area. At the lower sigmoid region, however, the character of arterial entry into the bowel changes. From the splenic flexure to the distal end of the sigmoid a continuous marginal artery descends close to the gut with arcades and free anastomosis. The marginal artery ends at the recto-sigmoid junction, as the superior hæmorrhoidal artery does not form arcades, and at this point vascular collaterals between lower sigmoid artery and superior hæmorrhoidal are not so free.

*Lower Sigmoid.*—Growths of the lower sigmoid present a more difficult problem and the methods employed fall into two groups :—

- (1) Miles <sup>21</sup> abdomino-perineal operation.
- (2) Various methods of reconstitution of the bowel continuity with preservation of the anal sphincters.

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for a permanent colostomy. In the second group, with retention of the anal sphincters, various methods have been attempted. As early as 1889 Hohnegg<sup>22</sup> pulled the open end of the proximal sigmoid through the anus after resection, a practice revived in recent years. Rutherford Morison and Lockhart-Mummery<sup>23</sup> sutured the sigmoid end to the stump of the rectum over a wide rubber tube. Crile<sup>24</sup> in 1920 did a primary suture to the rectal stump with a safeguarding proximal transverse colostomy. In the past decade renewed attempts in this direction have met with greater success, and the present-day anterior resection with primary anastomosis is becoming widely used. Wagensteen<sup>12</sup> and Dixon<sup>25</sup> have each reported a series of primary anastomosis with a mortality of 6 per cent. Standard and Mulholland<sup>26</sup> report a series of 40 cases with two deaths. Two cases have been done in my own wards recently, one dying of broncho-pneumonia and the other making an uninterrupted recovery. The chief difficulty in making the anastomosis is lack of accessibility, particularly in stout subjects, which may permit of the insertion of only one layer of sutures. The lack of peritoneal covering to rectum at the level of anastomosis is a hazard, as is also the infectivity of the perirectal tissues. Intestinal chemotherapy, however, reduces delay in healing and risk of leakage, and has converted a difficult and hazardous procedure into a routine operation.

Doubts have been expressed as to the adequacy of lymph drainage removal in this type of operation. It is generally agreed that lymph flow from the recto-sigmoid junction is mesial and upwards and that there is little downward extension. Where enlarged glands, however, are present in the normal lymph drain, a downward overflow must be suspected, and the abdomino-perineal excision will, in this type of case, be preferable to the leaving part of the rectum and its surroundings. Safety margins have been expressed in terms of centimetres, but the malignant cell, as we know it, has little regard for the metric system, and a wide series of five years' results is necessary before the success of this type of operation in removing lymphatic extensions can be determined.

#### PRE-OPERATIVE TREATMENT

Attention to the general condition of the patient is important. Most patients with cancer of the colon have a mild secondary anæmia, and in right-sided cancer this may be marked. A hæmoglobin standard of at least 80 per cent. should be aimed at before operation, and blood transfusion should be given pre-operatively to achieve this. More difficult is the problem of lowered plasma proteins. Binkley *et al.*<sup>27</sup> found that in cases of cancer of the colon hypoproteinæmia was present in 36 per cent. and that this incidence increased to 86 per cent. after operation, the serum albumen being mainly reduced. These findings have been confirmed and vigorous attempts have been made to raise the plasma protein. Intravenous transfusions of amino acids

in forms such as Casydrol have not, in the main, proved successful although in some individual cases clinical improvement has been noted. The present preparations are quickly excreted by the kidneys and little rise of serum protein has been noted in the blood plasma. My own experience of intravenously administered amino acids has been disappointing, but a newer preparation is being tried which has the advantage of slower excretion and may be more successful. Transfusion of blood plasma is also disappointing, large quantities raising the protein level by a small percentage only. A high protein diet is more effective but takes time. Dehydration is common, and the most practical results in the raising of the patient's vitality were attained by the daily intravenous administration of large amounts of glucose saline in the first four days of the preparation period. This is repeated after operation. A low residue diet is given and is continued after operation but diet should be adequate and have a high protein content and vitamin value. Fresh butter and eggs, oatmeal, milk and fruit juices are invaluable. Too low a diet is to be avoided and a moderate amount of faecal content at operation is preferable to a half-starved patient. Vitamins, especially C, D and K can be given, although their effect on wound healing has been disappointing. Laxatives are avoided and the bowel is prepared for operation in the following way: An enema is given on admission and is repeated the following day. On the second day the administration of sulfasuxidine is commenced in daily dosage of 0.25 gm. per kilo of body weight. This dose is divided into four equal parts and given four-hourly during the day. This treatment is continuous until the day of operation, which is generally on the fifth day after the commencement of chemotherapy. As the faeces become more fluid, natural motions tend to occur and the bowel at operation may contain a varying amount of soft greyish-black faeces, with low infectivity. An enema is given on the evening before operation.

*Operation.*—Anæsthesia is induced by pentothal sodium followed by nitrous oxide and oxygen, intravenous curare being used for muscle relaxation. This has been satisfactory and chest complications have been few. Intravenous transfusion has not been used during the operation, which should be done without hurry but as quickly as is compatible with efficiency. Resection of a large segment of colon with its lymph drainage takes up time and the last stage of anastomosis cannot be hurried. In resection of the left colon stretching of the anal sphincter helps the readier passage of flatus.

*Post-operative Treatment.*—In the absence of any degree of blood loss blood transfusions are seldom necessary. A glucose saline drip is given for the first twenty-four hours after operation and is continued so long as is found necessary. The Miller Abbot tube is only used if abdominal distension occurs and over-enthusiasm in suction is deprecated. The rectal flatus tube is passed four-hourly only under similar conditions and may aid in the passage of flatus. As far as

is possible the patient is given peace to recover. A high protein, low residue diet, as nourishing as possible, is given as soon as possible after operation and is continued for a week. Plasma protein level can be re-estimated and plasma and amino acids given intravenously but their value is doubtful and reaction may do harm. On the eighth day a gentle enema is given and is repeated on subsequent days until normal bowel movement is restored. Penicillin is begun immediately after operation as a prophylactic against bronchial complications, and administration of sulfasuxidine is continued for eight days, post operatively.

### OBSTRUCTION

The presence of obstruction makes primary resection anastomosis dangerous and, when it is marked, prohibitive. Obstruction, however, is a relative term varying from a mild hypertrophy and distension of the proximal segment to a wide distension of the whole colon proximal to the growth. In mild degrees of obstruction, the bowel at the site selected for section may be normal, and a primary anastomosis may be safely carried out. Where obstruction is marked, however, a period of drainage is necessary before resection can be attempted. The method adopted will vary with the site of the growth. In tumours of the right colon with its wide lumen and liquid contents, obstruction is uncommon and, where present, its extension proximally is limited by the action of the ileo-cæcal valve. The lower ileum is usually unaffected and can be safely anastomosed to the transverse colon by a side-to-side or end-to-end junction. Where obstruction is not complete a unilateral exclusive operation should be done, the ileum being severed completely and its distal end closed. Where obstruction is complete, however, a simple short-circuit prevents the danger of a closed loop with distension and possible gangrene. Hemicolectomy can usually be done in ten to fourteen days. Occasionally, however, incompetence of the ileo-cæcal valve may give rise to either acute dilatation of the terminal ileum or a thickened dilatation with congestion, making a short-circuit hazardous. Decision in this type of case may be difficult. Ileostomy is a misery to both patient and surgeon, with constant efflux of ileal contents and severe skin irritation. The alternatives are the risking of a short-circuit with unsuitable bowel, or an immediate hemicolectomy with exteriorisation and renewal of bowel continuity as soon as possible, the crushing of the spur being commenced within a week. Right lumbar drainage should be employed. Contra indications to immediate hemicolectomy are an inflammatory condition of the obstructed bowel, an adherent growth with surrounding infection, or any degree of general peritonitis. Each case must be judged individually and the varying risks assessed. It is fortunate, however, that this type of case is rare.

For growths distal to the middle of the transverse colon cæcostomy gives simple and efficient decompression. It is important that any

pre-resection colostomy should not interfere with later intestinal chemotherapy, and decompression rather than defunctioning should be aimed at. Extrusion of a whole loop of colon is undesirable. A cæcostomy, which allows onward flow of part of its contents, makes later chemotherapy possible. Before operation additional sulfa-suxidine in suspension can be introduced through the cæcostomy into the colon and similarly, per rectum, into the lower segment.

The value of decompression by suction through a swallowed tube which reaches the lower ileum or cæcum is on trial. Tubes of various types, the Miller Abbot, Levine and Harris, can pass from the stomach into the lower ileum and cæcum and suction of bowel content can decompress the obstructed bowel. The problem is, how far their use can convert an obstructed colon into one which can safely be subjected to a primary resection anastomosis, making pre-operative colostomy unnecessary. Whipple<sup>28</sup> has reported good results from its use in obstructive lesions in the right colon, permitting primary resection anastomosis to be done, but much wider experience of its use is necessary for a determination of both its scope and its limitations. Assessment of its value is difficult as the condition of the colon before the institution of suction is a matter of conjecture rather than of knowledge.

### CONCLUSIONS

In conclusion, progress during the past ten years gives promise of a growing safety in resection with primary anastomosis of the colon and the attainment of a mortality rate more approximating that of an ordinary major operative risk. Many factors have contributed to this, including greater attention to the general condition of the patient with increased pre- and post-operation precautions, and safer methods of anæsthesia. The two factors which predominate, however, are :—

- (1) A greater appreciation of the necessity for vascularity and viability in the cut edge, with elimination of clamps and constricting types of suture.
- (2) The introduction of intestinal chemotherapy which makes the healing of the anastomosis one of first intention rather than that of an infected wound.

It must be remembered that modern operative methods are based on experience accumulated over the past half century by the endeavours of three generations of surgeons, with varying hopes and disappointments, failure and success. Among these the names of Francis Caird and David Wilkie, of this distinguished school, rank high.

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## INTRACRANIAL TUMOURS IN THE AGED

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It is symptomatic of the times in which we live that I have chosen this subject for investigation, because all the evidence points to an increasing proportion of our population living to a ripe old age. Obvious factors in this trend are the recent advances in medical science, for example, the introduction of the sulphonamides, penicillin and streptomycin, and from another angle, the rapidly expanding social services. Indeed some cynics have observed that these developments make it rather difficult to die nowadays, but it is clear that clinicians are going to have to concern themselves more and more with the problems of advancing age. It is of course impossible to define old age because one man may be old at forty and another young at seventy, but for practical purposes most of us have our private standards for the end of middle life and the beginning of senescence, and this paper is concerned with subjects over the age of sixty. I was supported in this choice by looking through the material in the Nuffield Department of Surgery in Oxford—which is largely concerned with neurological surgery—when I found that during the war and especially during the heat of the conflict, we had almost no patients with brain tumour over the age of sixty: there were indeed many patients older than that, but for the most part they were suffering from trigeminal neuralgia, spinal compression, and subdural hæmatomas, *i.e.* conditions which are known to be generally remediable. This suggests to me that practitioners who diagnosed brain tumours in patients over the age of sixty regarded their life as spent, and did not consider it worth while submitting them for the rather elaborate investigations and treatment which such cases often entail. Such an attitude was probably justifiable, and if there was any question of a conflict, say, between pediatrics and this new science of geriatrics, the children should be given the benefit every time. In normal times, no such conflict should arise and the complete health service should provide equal amenities for all age groups.

In our material I found that there were 86 cases of intracranial tumour in subjects over the age of sixty. To deal briefly with the pathology, as with the treatment of neoplasms at any age, the success of our efforts depends largely on the nature of the tumour.

A Honyman Gillespie Lecture delivered in the Royal Infirmary on 21st October 1949.

It will be seen from Table I that 45 per cent. of them were in the glioma series, and that more than half of them were spongioblastoma multiforme, which is one of the most malignant types. The other gliomas are malignant in the sense that they are infiltrating tumours, they usually cannot be completely removed, and recurrence after operation is the rule. It is interesting that in this series there were no examples of ependymoma, or medulloblastoma, and only one oligodendroglioma—all common tumours in childhood and early adult life.

TABLE I

*Pathology of 86 Intracranial Tumours in Patients over Sixty Years of Age*

Type		No. of Cases
Glioma.—		
Spongioblastoma multiforme	. . . . .	22
Astrocytoma	. . . . .	10
Oligodendroglioma	. . . . .	1
Unspecified	. . . . .	6
Total . . . . .		39 (45 per cent.)
Metastatic carcinoma.—		
From lung	. . . . .	5
Accessory sinuses	. . . . .	4
Prostate	. . . . .	1
Colon	. . . . .	1
Stomach	. . . . .	1
Thyroid	. . . . .	1
Total . . . . .		13 (15 per cent.)
Acoustic neurinoma	. . . . .	6
Pituitary adenoma	. . . . .	7
Craniopharyngioma	. . . . .	3
Hæmangioblastoma	. . . . .	3
Meningioma	. . . . .	15
Total . . . . .		34 (40 per cent.)

Metastatic cancer accounted for 15 per cent. of the cases, the lung coming first as the primary site. This figure is a little higher than in the earlier age groups, as would be expected, but it does not represent the total incidence of metastatic carcinoma of the brain because, when there is an obvious primary growth with other metastases, the advent of a metastasis in the brain generally does not demand admission to a neurosurgical clinic. In most of our cases no primary growth had been detected, and more often than not it was for lack of having had the chest X-rayed.

The remaining cases comprised a miscellaneous group of acoustic neurinomas, pituitary tumours, meningiomas—but adding up to a significant total of 40 per cent., significant because these tumours are essentially benign and remediable.

Table II shows the topographical distribution, and it is of interest that in 83 per cent. of the cases the lesion was above the tentorium. That is to say that cerebellar tumours on the whole are rare in old age, whereas they make up a large proportion of the cases in children and young adults. This fact is related to the infrequency of ependymomas, medulloblastomas and cystic astrocytomas in old age, whereas they are the commoner tumours of childhood.

TABLE 2

Cerebral hemisphere.—							
Frontal . . . . .							18
Temporal . . . . .							22
Parietal . . . . .							8
Diffuse and multiple . . . . .							4
Basal ganglia . . . . .							4
Total . . . . .							56
Pituitary and supra-pituitary . . . . .							10
Skull base . . . . .							6
Brain stem . . . . .							1
Cerebellum . . . . .							6
Cerebello-pontine angle . . . . .							7

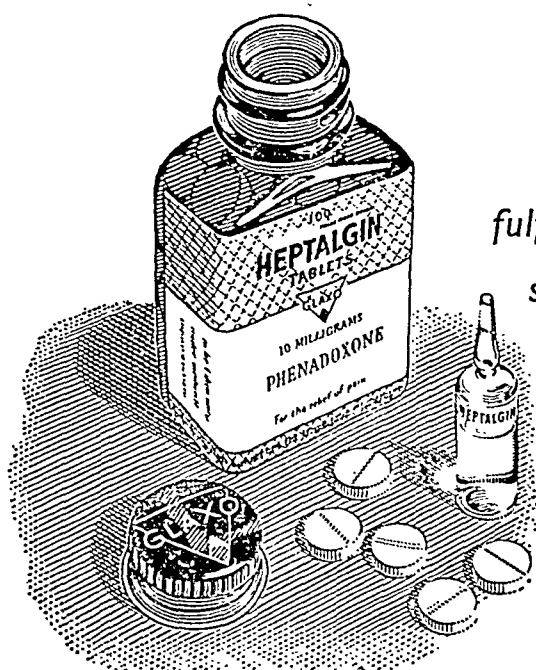
83 per cent.  
above tentorium

In childhood and early adult life the diagnosis of intracranial tumours is generally straightforward because in an otherwise healthy subject there is little else that can produce symptoms and signs of a brain tumour. There is a group of symptoms due to the general effects of increased intracranial pressure, and another group due to the local effects of the lesion. The intracranial pressure may be increased by any expanding lesion because the capacity of the cranial cavity is just sufficient to house the brain with its blood vessels and meninges, and the cerebro-spinal fluid. A space-occupying lesion first displaces cerebro-spinal fluid from the sulci and the large cisterns at the base of the brain and it is only when this extra space has been used up that the pressure begins to rise. In children the onset of symptoms of increased intracranial pressure may be delayed by the fact that the skull can expand by separation of the sutures, and considerable enlargement of the skull may occur before there is any other objective evidence of increased pressure or any symptoms. But in adults no such increase in the cranial capacity can occur, and as soon as an expanding lesion has reached the limit of compensation afforded by displacement of cerebro-spinal fluid, symptoms of increased pressure present themselves. There is headache, dull and intermittent at first, becoming more severe, frequent and almost continuous. It is apt to be worse on waking in the morning, and aggravated by coughing and straining. Vomiting, slowing of the pulse rate, drowsiness, incontinence, stupor and coma are the well-known concomitants of

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increased pressure, and they can be produced by any expanding lesion, whether neoplasm, abscess or blood clot. Objectively we can determine the fact of increased pressure by observing papilloedema or by spinal manometry, although both of these methods have their limitations. Thus flagrant papilloedema can occur in cases of venous obstruction in the cranium when there is little or no rise of intracranial pressure, and this will be most familiar to you in these strange cases of "otitic hydrocephalus" or cerebral thrombophlebitis which are usually due to some infective process in the face or skull. And although the spinal fluid pressure is generally raised in cases of brain tumour, there are many cases in which it is normal. One explanation of this fact is that the temporal lobes may be impacted in the tentorial notch, or the cerebellar tonsils in the foramen magnum, acting as a stopper so that the pressure measured in the lumbar theca is not a true index of that within the cranium.

As an example of this anomaly about intracranial pressure, there is the case of a man of 61 (R.I. No. 2085/38) who was admitted in May 1938. For about a year he had had a little headache, and for two months some giddiness on sudden changes in posture. It was this symptom which led to his giving up his work in an engineering factory as he was afraid that he might fall into the machinery. From that time he deteriorated rapidly: he became forgetful, apathetic, occasionally incontinent and rambling in his speech. He was admitted to another hospital ten days before he came to us and got much worse after a lumbar puncture, notably in severe headache, stiffness of the neck and mental confusion, although he had improved to some extent by the time he got to us. On admission, he looked grey and wasted, was doubly incontinent, but was quite alert. The neurological examination revealed nystagmus on looking to both sides, a little impairment in the trigeminal zone on the left side, slight deafness of the left ear, and slight ataxy of the left limbs but no papilloedema. The clinical evidence thus pointed to a lesion in the left side of the posterior fossa but the short history sounded ominous. We spent some time in searching for a silent primary tumour but no such tumour could be found. In the course of the investigations a lumbar puncture was done and the pressure was only 65 mm. with a normal response on jugular compression. The fluid contained 75 mgm. protein and there was a slight change in the Lange curve but the serological tests for lues were negative. He was seen by an eminent neurologist, who, while agreeing about the left cerebellar lesion, argued that the absence of papilloedema and the low spinal fluid pressure made a tumour most unlikely and that an atrophic lesion was more likely, with syphilis a possibility. He advised a course of mercury and iodide but within a week the patient's condition had deteriorated to the point when it was obvious that he was going to die if something else was not done so we decided to explore the posterior fossa. At the operation, both ventricles were found to be capacious and the pressure was over 500 mm. When the dura in the posterior fossa was opened, the cerebellar tonsils were found to be jammed in the foramen magnum, and despite the fact that the ventricles had been tapped the cerebellum was bulging and tight. The lesion proved to be a cystic hæmangioblastoma in the left cerebellar lobe which could be removed with complete recovery and return to full work.

The local effects of an intracranial tumour depend to a large extent on the site of the lesion, and there will be varying degrees of paralysis, sensory disturbance, defects of the visual fields, aphasia and dementia, depending on which part of the cerebral hemisphere is involved. In the cerebellum, there are chiefly disorders of co-ordination of the limbs and eye movements and paralysis of the lower cranial nerves. These signs may be so gross that they need only to be looked for by the tyro, or they may be so slight as to almost escape detection by the experienced examiner, and it is this which contributes so much to the interest of clinical neurology.

Commonly, one or other group of symptoms predominates. That is to say that in one case there may be severe headache, vomiting and papilloedema with little in the way of neurological abnormalities and in another there may be gross aphasia, hemiplegia, hemianopia with little headache or other symptoms of increased pressure. There are, of course, exceptional cases in which there is a massive brain tumour with little in the way of symptoms or signs. Recently we had a young man who was known to the police as an epileptic, and was on several occasions brought into the casualty department after a fit. On the last occasion an enthusiastic house surgeon happened to look at his fundi, found intense papilloedema, and the subsequent investigations disclosed a massive glioma occupying the greater part of both frontal lobes.

This brief description applies generally to cases of brain tumour in children and young adults. In what way is it modified by advancing age and why is it that tumours in the aged are worthy of a special study?

It is common knowledge that as we enter the period of senescence, the brain tends to shrivel up to some extent, and "senile atrophy" is a commonplace in the post-mortem room. In advanced cases, the brain may remind us of nothing so much as the kernel of a walnut, and even in slight cases the shrinkage is obvious to the naked eye. This shrinkage is a general one so that not only are the ventricles a little larger than normal, but the whole external surface of the brain is affected. This means that the subarachnoid space is correspondingly larger, and that if a space-occupying lesion begins to develop there is much more room available than in a younger subject. The effect of this is that a tumour may attain a considerable size and produce a gross disability or even death before there are any symptoms or objective evidence of increased pressure. In about 40 per cent. of this series, there was no papilloedema or other evidence of increased pressure when the patients first came under observation.

Secondly, the difficulties of diagnosis are enhanced by the fact that the longer we live the more complex become the pathological possibilities. The symptoms which I have mentioned above would point clearly to a brain tumour in a child or young adult, but in old age, when the machinery is beginning to wear out, these same symptoms may be due to disease of one or more systems other than the nervous

system. To take an example, the description of the headache of increased intracranial pressure would apply just as well to the headache of arterial hypertension in which there may be no increase in intracranial pressure. Headache, vomiting, hiccough, drowsiness and coma are common symptoms of uremia. Papilloedema may occur in such relatively benign states as emphysema. The spinal fluid pressure may be elevated in cases of gross obesity. Rarefaction of the dorsum sellae, which is a common radiological index of increased pressure in young adults, is unreliable in old age because the whole base of the skull becomes a little thin and the sella may be decalcified in normal subjects. And when you add to this the knowledge that vascular lesions of the brain are after all the commonest cause of hemiplegia, aphasia and the like in elderly subjects, and that arterial disease can produce abnormalities in the retina which may so closely resemble the papilloedema of increased pressure as to confuse even an expert ophthalmologist, it is obvious how much more complicated the clinical picture becomes. And there always remains the possibility of two disease processes co-existing; *i.e.* a person may have a brain tumour and at the same time have cerebro-vascular disease or some other disease which may simulate a brain tumour.

Thus in February 1948 I saw a man of 61 (R.I. No. 87090/48) who for a year had had a little headache, and had been noticed by his business associates to be losing something of his normal acumen. There was nothing more to it than that but three months before I saw him he had an attack of pneumonia and phlebitis in both legs which had, if anything, accentuated his intellectual deterioration. He was seen by several consultants who ascribed this to cerebral arteriosclerosis. His own doctor was unwilling to accept this verdict because the blood pressure was 140/105. I could find no focal neurological abnormalities of any kind, but a lumbar puncture showed that the pressure was 250 mm. and the fluid contained 70 mgm. protein. This seemed too little evidence to proceed on, so I advised waiting for two or three months to see what happened. He continued to deteriorate, and by early May it was clear that a full investigation was called for so he was admitted to hospital. By this time, he had considerable papilloedema, and there was a slight right hemiparesis. More important, we observed several epileptic attacks while he was in hospital, characterised by turning of the head and eyes to the right side, clonic movements of the right side of the face and right upper limb, and there was a transient aphasia after the attacks. The picture now was that of a left frontal tumour, but an arteriogram showed no displacement so a ventriculogram was done. This showed a symmetrical dilatation of the lateral ventricles without displacement, and enlargement of the third ventricle, that is, the picture of a subtentorial lesion without any evidence of a left frontal tumour at all. A cerebellar exploration was done and an angiomatous malformation was found. During the operation all the arteries in the scalp and suboccipital muscle stood out like pipestems and those in the cerebellum could be seen to be similarly affected. The patient thus did have cerebro-vascular disease in addition to an expanding lesion, and the epileptic attacks were probably the response of arteries already beginning to feel the strain to an added burden, that of increased intracranial pressure. The operation in this case had the effect of relieving the symptoms



of increased pressure but recovery is short enough of complete to have made him retire from work, although he is able to lead quite an active and happy life in his retirement.

So much for the difficulties. Fortunately neurology has developed to the point at which it is possible to make the diagnosis in most cases. In addition to the clinical investigations, there are available special techniques such as ventriculography and arteriography, which in most cases will give the answer. In our clinic, the most common diagnostic problem in this age group was that of differentiating between brain tumour and cerebro-vascular disease. In general, cerebro-vascular disease is a matter of sudden episodes rather than steady progression as in the case of tumours. These episodes bespeak small infarcts or less commonly, hæmorrhages, and they may produce multiple lesions in the brain which on the whole are unlike the effects of a neoplasm, as in the latter the signs can usually be explained on the basis of a single lesion. Moreover, some degree of recovery is common in vascular lesions whereas the abnormalities caused by neoplasms are generally progressive. There is often evidence of vascular disease in other systems, but it should be noted that the cerebral vessel may suffer first and most : thus a patient may die from a cerebral thrombosis or hæmorrhage and at autopsy the cerebral vessels found to be grossly diseased whereas those in the rest of the body are reasonably healthy. X-rays of the skull are generally of little help unless they show displacement of the calcified pineal gland which indicates an expanding lesion in one or other cerebral hemisphere. Examination of the cerebro-spinal fluid is of some help because in cerebro-vascular disease both the pressure and analysis are usually normal whereas in tumours there is commonly some increase in the protein content of the fluid even though the manometric observations may be open to the suspicions already mentioned.

Another common problem in differential diagnosis has been that of subdural hæmatoma. This is an affection which is quite common in elderly subjects and usually is the sequel of a mild head injury, as a result of which a small vein on the surface of the brain is torn and continues to ooze until a large clot is formed on the surface which compresses the hemisphere generally. It is a strange fact that such a lesion produces general rather than focal signs. Headache is common, but more characteristic is variable drowsiness. Thus we have frequently been asked to admit patients in coma to find them quite bright and alert by the time they get to us, but they may shortly relapse into deep stupor from which they again recover spontaneously. This variability does occur in brain tumours too but it is more characteristic of hæmatomas. Of focal signs one of the most common is bilateral ptosis and defective upward movement of the eyeballs, signs commonly regarded as being due to a mid-brain lesion and in these cases probably being due to compression against the free edge of the tentorium as they clear up dramatically once the hæmatoma is evacuated. Gross



FIG. 1.—Antero-posterior ventriculogram, showing slightly dilated ventricles without displacement. (Case No. R.I. 55780/46).

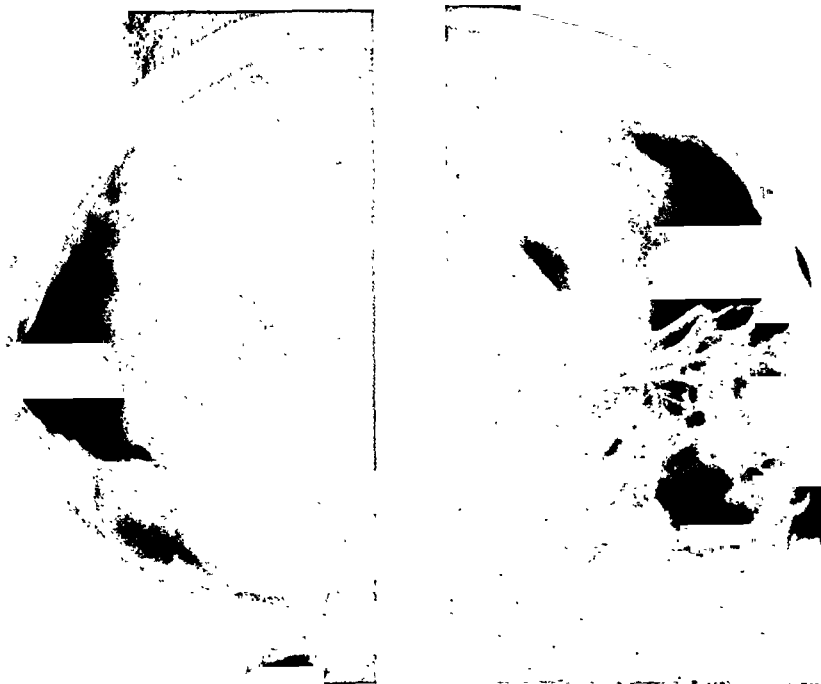


FIG. 2.—Composite lateral ventriculogram, showing cerebral atrophy and slight ventricular dilatation. (Case No. R.I. 55780/46).



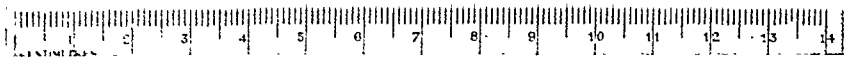
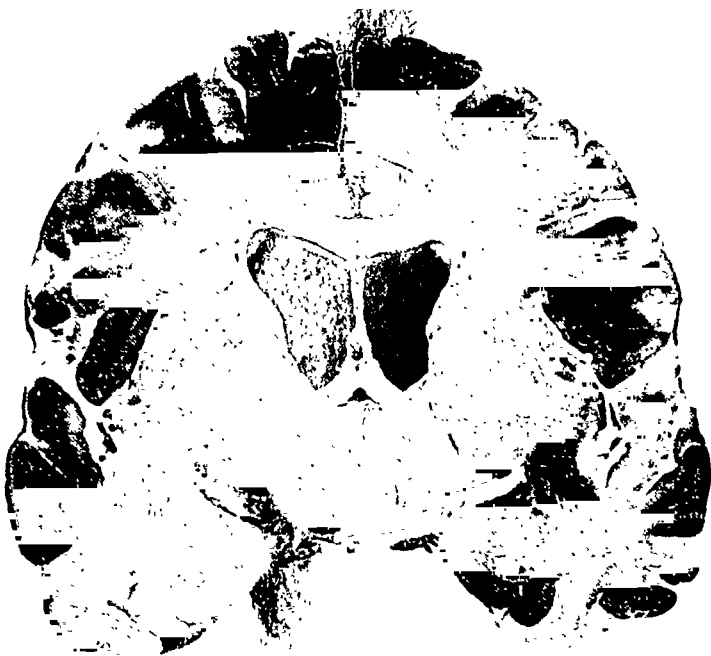


FIG. 3.—Coronal section of brain, showing astrocytoma of hypothalamus.  
(Case No. R.I. 55780/46).

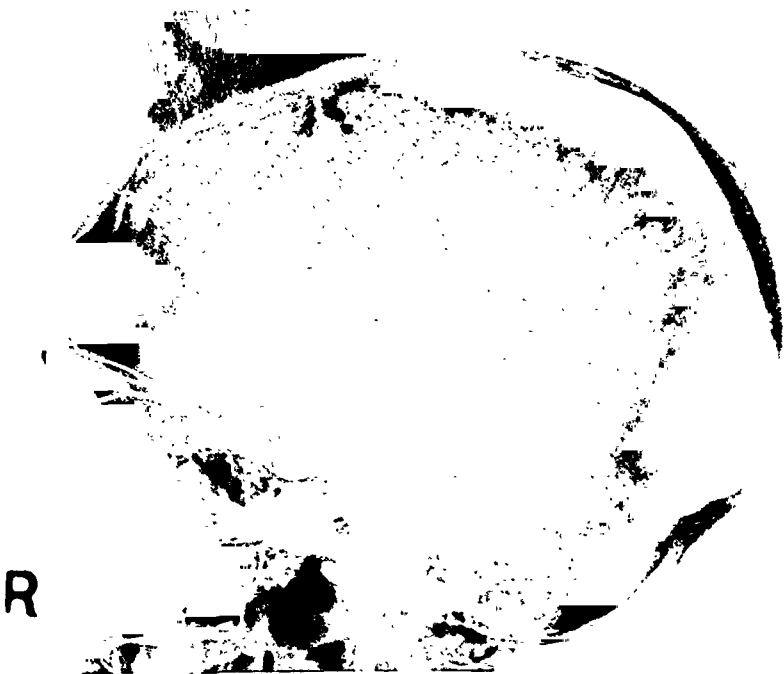


FIG. 4.—Calcified Mass in anterior cranial fossa.



hemiplegia and sensory defects are uncommon, as is epilepsy, and when there is a hemiplegia it may be an ipsilateral one due to compression of the opposite crus against the edge of the tentorium. These lesions are generally known to be curable and it is natural that the conscientious practitioner gropes at the story of any head injury when one of his patients presents signs and symptoms of cerebral derangement. The diagnosis can be made in these cases by ventriculography or arteriography, both of which show characteristic features, but it is as easy to make burr holes for inspection of the subdural spaces, and the clot can be evacuated through them. There are few lesions which respond so dramatically and completely to this simple procedure.

Then there is the group of senile epileptics and dementia which may be due to cortical atrophy or to neoplasms. In our experience epilepsy coming on for the first time late in life is more often due to a neoplasm than any other lesion and this possibility must always be borne in mind. On the other hand a slowly progressive senile dementia without obvious neurological abnormalities is usually not due to a neoplasm.

Turning now to the diagnosis, when a neoplasm is suspected what special investigations can be done to prove it? Ventriculography is perhaps the most generally useful and in most cases of doubt it will give the answer. But not always, as in the following case:—

A woman of 77 (R.I. No. 55780/46), was admitted on 3rd April 1946. She had apparently been in exceptionally good health until five days before admission when she said that she felt a little off colour and drowsy and went to bed in the afternoon. The next morning she said that she felt well and was up and about doing her housework, but in the afternoon she became confused and again very drowsy. She was put to bed, and continued to deteriorate from that time. The most striking feature was variable drowsiness: at times she was apparently almost comatose, and at other times quite alert but very confused and irrational. She had not complained of any headache.

There was nothing in the previous history except that two weeks before the onset of symptoms she slipped on the stairs and struck her head in falling: she was dazed for a time but there were no sequels and nothing was thought of the injury at the time. Knowledge of this injury very rightly raised the question of a subdural hæmatoma and she was sent to us with that diagnosis.

On examination she looked quite well and at the time was quite alert. She was very confused, however, disorientated in time and space and incontinent. There was no aphasia, no papilloedema and no defect in the visual fields. There was slight bilateral ptosis, giving her a very sleepy appearance even though she was quite alert. There was some impairment of upward movement of the eyeballs, but no other definite neurological abnormality, that is, no hemiplegia, alteration in the reflexes, or sensory disturbance. The general examination revealed no gross abnormalities: blood pressure was 110/70, and X-rays of the chest showed calcification of the aorta. X-rays of the skull were normal. The spinal fluid pressure was 110 mm. The fluid contained 200 mgm. protein and 35 lymphocytes.

The findings on examination were consistent with a subdural hæmatoma so frontal and parietal burr holes were made, and no hæmatoma was found. Instead the cortex was seen to be shrunk and the subarachnoid space greatly distended so that 10-15 c.c. of fluid could be aspirated with ease. We subsequently filled the ventricles with air, and the skiagram showed slightly dilated and symmetrical ventricles and a gross excess of air disposed over the surface of the brain (Figs. 1 and 2). It was thought that this indicated a state of cerebral atrophy and no further treatment was carried out. She died five days later—ten days from the very onset of the illness—and at the autopsy, the lesion was found to be an astrocytoma in the hypothalamus and lower part of the 3rd ventricle (Fig. 3).

The introduction of arteriography has been another step forward because with this technique we can often determine the presence and location of a tumour, as well as its nature, because different types of tumour have different vascular patterns. But there are some situations in which this technique may not give as much or any more information than ventriculography, and commonly we have to employ both methods, and there are very few cases which will elude them. Occasionally, in doubtful cases, an exploratory craniotomy is called for, but with refinements in diagnostic methods this operation is becoming progressively less frequent.

Once the diagnosis has been made, what should be done? It has been seen in Table I that 45 per cent. of these tumours were in the glioma series, and that more than half of them were spongioblastoma multiforme, which is one of the most malignant types. The others are malignant in the sense that they usually cannot be completely removed, and recurrence after operation is the rule. These characteristics apply as much to this type of tumour in younger subjects, but the problem of treatment is different in that it may occasionally be valuable to give a young person an extra three or four years of life to discharge certain commitments, whereas this is rarely so in old age. It has been seen too that 15 per cent. of the cases were metastatic cancer, the lung coming first as the primary site. Taking these two groups together, 60 per cent. of them are malignant in either the clinical or the pathological sense, and my own feeling is that surgery has little to offer them. But it is important to verify the diagnosis because all of the clinical evidence and the special investigations may point to a malignant tumour and yet it prove to be benign. We make a practice of making a burr hole over the lesion and putting in a small cannula to get some of the tissue for histological examination. This can be spread on a slide, much as in making a blood film, stained with toluidine blue, and in over 90 per cent. of cases an adequate histological diagnosis can be made. In cases in which there is uncertainty, for example, when the tissue proves to be too tough to deal with in this way, we occasionally have to resort to exploratory operations. It should be known that such biopsies carry some risk to life; the needle may start a little bleeding which goes on to cause an additional rise of pressure

which may be fatal. In cases of advanced malignant tumours, this result may be merciful, but in the case of benign tumours it can be averted by proceeding straight away with the operation for removal of the tumour.

The remaining 40 per cent. of these tumours comprised acoustic neurinomas, cerebellar hæmangioblastomas, pituitary tumours, and meningiomas—tumours which are essentially benign and which respond well to operation, either for complete extirpation or partial removal, to give a long period of useful survival. This applies particularly to the 17 per cent. of meningiomas, which can generally be completely removed with more or less complete recovery of function.

Old people stand these operations very well. Indeed there were no operative deaths in the group of benign tumours. We use general or local anæsthesia on the same indication as in younger subjects, and with no more post-operative complications, although in elderly subjects we do encourage early mobility after operation to lessen the risks of hypostatic pneumonia, and we often get these patients out of bed on the day after operation if their general condition allows it. It is clear too that active physiotherapy, including breathing exercises, plays a large part in a smooth convalescence.

What are the functional results like? In the majority of cases they are as satisfactory as in younger subjects, but just as old people tolerate head injuries less well than younger ones, there are occasional recoveries which are far short of complete. I think this applies particularly to cerebellar deficits; a child may be left with a gross cerebellar disability following the removal of a benign cerebellar tumour and in time learn to master it almost completely. A young adult may also make a very satisfactory adjustment by the use of his intellect much as in learning to use an artificial limb. But gross ataxy often defeats an old person completely. Two patients with acoustic tumours which were removed with satisfactory neurological results remained more or less invalid because they could not cope with the ataxy, despite encouragement, formal exercises and the like. Such results do occur in younger subjects and they do not detract from the argument that all of these benign tumours should be treated energetically and with confidence. I say all, and yet not all of them do need operation. Four years ago, I saw a well-preserved lady of seventy-eight who had had occasional epileptic attacks for ten years, but no symptoms in between the attacks, and there were no abnormalities on examination except bilateral anosmia. X-rays of the skull showed an ovoid calcified mass in the anterior cranial fossa (Fig. 4) which we take to be an olfactory groove meningioma. She is still able to lead an active and useful life, and removing this tumour could neither guarantee cessation of the epilepsy nor bring about any improvement in her sense of smell. Similarly we have several elderly patients with clear signs of an acoustic tumour who have been under periodic observation for periods up to ten years without any evidence of progression or signs of



increased pressure, or indeed any real disability, and it would obviously be meddlesome to interfere with them.

#### SUMMARY

1. Intracranial tumours in the aged do not conform to the more familiar clinical picture seen in children and young adults, notably in that the advent of pressure signs and symptoms may be late or may not occur at all.

2. The difficulties of diagnosis are enhanced by the fact that other diseases, notably cardiovascular disease, may produce signs and symptoms very much like those of brain tumours and the differential diagnosis may demand all the refinements of modern medicine.

3. About 60 per cent. of the tumours are malignant in the sense that they cannot be completely removed, and surgery has little to offer them except palliation.

4. In the remaining 40 per cent. of benign tumours, the results of operation are as good as in the younger age groups, and they justify the slightly greater risk of any major procedure in old age.

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## DIASTOLE

By BRUCE WILLIAMSON, M.D. Edin., F.R.C.P.

THE subject of my discourse this evening is one of those items in medicine and to some extent in cardiology to which only casual notice is given both in the lecture room and in the textbooks. It is the name applied to a gap which succeeds the active work of the heart, namely systole, and from what I encounter in post-graduate work it is also a gap in the average knowledge on the heart. There would appear to be a tacit agreement between the heart and the teacher that diastole is a period of rest for both of them and also for the student.

My interest in diastole dates back many years to a statement by Osler, whose centenary occurred this year, "that diastole is less regarded but that it might be well to give it more attention." The word "diastole" in derivation means to set or send apart or to dilate; a somewhat negative state is implied which is far from the truth.

If we consider the two states of the heart, namely systole and diastole, a fundamental difference stands out clearly. It may be stated that upon systole depends the well-being of the various systems in the body—the ease or dis-ease in which the different organs carry out their specific functions. Whereas, upon diastole depends the efficiency of the heart or myocardium itself. There are thus two distinct factors in the cardiac cycle which may be classified as external or systolic and internal or diastolic and of these two phases in the cardiac cycle the internal or diastolic is of greater import *quæ* the heart. There may be many defects in the systolic phase without much loss in efficiency in the cardiac output as we well see, for example, in valvular disorders which exist over scores of years in the life of a cardiac patient. The same may not be said of the diastolic phase. Disorders in function within the myocardium during diastole reflect themselves within a short period, in time and to a degree directly proportional to the departure from normal diastolic physiology. So, far from diastole being a negative phase the truth is that diastole governs systole to a great extent. A little reflection and correlation of facts well known to you will, I hope, bring conviction, and I must ask indulgence if I recall to your memory some of the less complex and simple or elemental facts. It has been termed "cardiology without tears" and it may afford you moments of relief in simple cerebration from other cardiac problems such as the perplexities in electrocardiography which impede your academic path.

Let us now recall the significant facts relating to diastole. The first and most important factor is that the coronary circulation, apart

from surface vessels is almost exclusively diastolic in time. This observation dates back to 1628 when Harvey observed the heart in systole to be pale and that the colour deepens between contractions of the heart. If we reflect for a moment upon the force of the myocardium and the peculiar pattern arrangement of the myocardial fibres, it must be agreed that when the myocardium contracts, the lumen of the intra-mural vessels cannot be other than in a state of obliteration (Fig. 1). Evidence of this is seen in the pallor of the heart muscle in systole; also during this phase the heart has the consistency of a solid rubber ball to manual palpation.

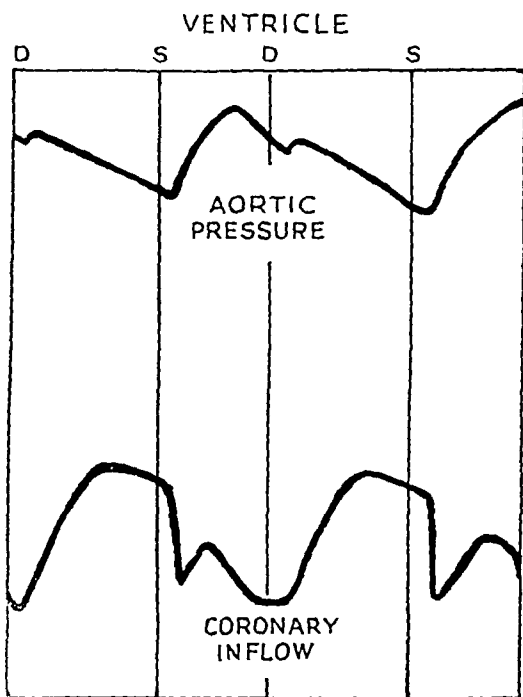


Fig. 1.—Changes in coronary flow during phases of cardiac cycle.—*Upper curve*, aortic pressure tracing. *Lower curve*, coronary inflow. *Vertical lines*, D is diastolic onset. S is systolic onset. Ventricular in time.

(After Green, Gregg and Wiggers, *Am. J. of Physiol.* (1935), 112.)

An important factor in the coronary circulation is the part played by the diaphragm formed by the closure of the aortic valve. During systole blood is ejected into the aorta, and the rebound or recoil of the elastic aorta to this thrusting column of blood throws down the aortic cusps to form the aortic diaphragm which cuts off or isolates the left ventricle. It is in this phase that the main stream of blood begins to enter the coronary vessels which have been emptied by the pressure of previous systole. The perfection of the aortic diaphragm thus plays a very important part in deciding the coronary blood pressure and in aortic regurgitation this is adversely effected despite adequate compensatory ventricular hypertrophy. Herein lies the clue to the real significance of any aortic reflux into the ventricle. Aortic

regurgitation must in the long run favour fibrosis from loss of the capillary fields in the myocardium following anoxæmia from loss of coronary pressure. Slow atrophy ensues and vicarious fibrosis eventually leads to one form of fibroid heart.

Now let us consider the true place of diastole in the cardiac cycle. It has been found that the duration of the ejection phase of systole varies little from  $\cdot 2$  to  $\cdot 25$  second and for practical considerations

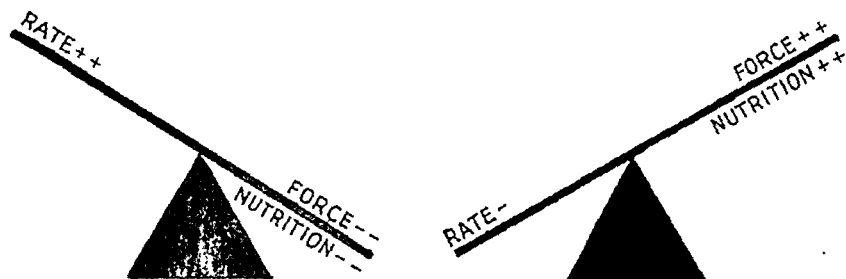


FIG. 2.—Schematic presentation of the reciprocal action of rate and force.

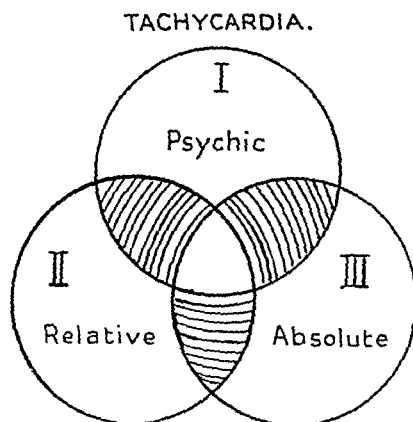


FIG. 3.—Schematic presentation of tachycardia show composite types in order of gravity. I. tachycardia due to psychic causes; II. tachycardia called in to meet an additional cardiac load; III. tachycardia compensatory to a fall in stroke-volume. Overlapping areas indicate more than one factor operating simultaneously. (From the Author's textbook *Vital Cardiology*. E. & S. Livingstone, Edinburgh.)

we may look upon systole as a constant. This being so it follows that the duration of diastole varies adversely with the cardiac rate. This constancy of systole in duration means, neither more nor less, than that the duration of diastole in the normal day depends upon the number of contractions the heart takes to meet the circulatory demands (Fig. 2) and, as we have seen, the coronary circulation is diastolic in time. Therefore all increases in rate are found at the expense of diastole and it follows that the coronary circulation is curtailed in time. This shortening of diastole does not amount to much in the ordinary fluctuations in rate over the twenty-four hours, for the slowing effect

of the vagus over-night fully compensates by granting to the myocardium more than ample diastolic duration to correct any metabolic demands not met completely during the day. When, however, there is *sustained tachycardia*, especially of high frequency, the shortening of diastole may be such as to curtail the coronary circulation (Fig. 3) to the point of endangering the myocardial nutrition with resultant accumulation of incompleated metabolites in the myocardium. This we meet clinically in the ordinary congestive heart failure which is usually accompanied by tachycardia of a hundred or more beats to the minute. How soon this tachycardia will induce coronary insufficiency depends upon several factors such as the myocardial reserve, the degree of arterio-sclerosis and the quality of blood as a vehicle of metabolites. With such potential for mischief, tachycardia should always excite the liveliest clinical interest in adult hearts for, by appreciation of its direct effect on the coronary circulation, through curtailment of diastole, heart failure may not only be forecast with a considerable degree of certainty but forestalled by appropriate action to restore to the myocardium the time element in its own metabolic processes. The heart rate in its effect on diastole is therefore worthy of our very serious attention, and it could be an alternative title to this lecture.

### ECONOMY OF FUNCTION

A first matter of importance is the realisation that the heart does not conduct its affair with any regard to economy.

Permit me to divert a moment on this idea of economic function. Nature has so arranged in the layout for control of systems that each and every one of the organs of the body under the autonomic system receives intimation of the body requirements through the sympathetic and vagus but the stimuli received do not appear, except rarely, to reflect the niceties of the varying demands. In the perfectly functioning body—an ideal state impossible to these artificial days of hectic demand and supply—the stimulus conveyed to any system should produce the exact response to fulfil the demand. This state is indeed rarely encountered—and never in clinical medicine—that is, the perfect balance in autonomic control. Under present-day civilisation we are happy to have the normal paths available and the stimuli transmitted cause reactions which reflect the degree of departure from the ideal. A simple example may be illustrated in the personal reactions to a sudden clap on the back. The results range from imperturbability to a leap in the air. Or, take the reactions to an unexpected telegram; this may be met with simple curiosity or the response may be flushing and great over-action of the ventricles, with palpitation and pulsation felt all over the body. The cardiac output in the latter circumstance would perform much manual labour. Or, recall the cardiac state within a few yards of the door of an oral examination in your final—

that perhaps will bring home to you what I mean by uneconomic function. The exertions of the myocardium at these moments could well provide circulation for the hundred yards in ten seconds. No doubt you could furnish scores of other examples, such as vivid dreams and other crises which involve no muscular energy of any moment, yet the blood velocity and pressure obtain to such figures as to make possible the rupture of blood vessels. I think you will agree that the heart knows no economies, political or otherwise. Here we have a date with the heart only, but it would not take long to provide you with examples to prove that nature ignores economic function in every system in the body. Allow me just one example extra-cardiac. I will choose the hyperchlorhydria in the anxiety state. Worry alone can readily produce a peptic ulcer clinically perfect. This question of uneconomic function has not yet been recognised in clinical medicine, yet I venture to say that it has a profound bearing on therapeutics for there is no surer path to derangement of function in any system than continued or sustained uneconomic function. Why it does not obtrude vigorously into the clinical field is because of the provision of a great reserve in all systems to meet the uneconomic demands which are made. Indeed, it is our major function as physicians to advise on economy of cell function for we cannot alter the specificity of human-cell function. Disease arises from over-action of cells or under-action down to cessation of function. We cannot alter anything by treatment beyond influencing the rate of function. Realisation of this early on in your careers provides a new and satisfying outlook on medicine and forestalls the disappointment and discouragement which follow the dispensation of faith, hope and charity in a bottle which, despite the label, is still unshaken.

Let us return to the heart of things. The heart knows no economy and the effect is seen mainly in diastole. Nor is the heart a seat of intelligence; far from it in fact—at times it proceeds on its way with a temerity only exceeded by its myopia both as regards its own welfare and that of its owner. Have we not all seen countless cases of hearts taking a hundred and twenty beats to do no more than half its job which, in a day or two, with the aid of digitalis, it executes perfectly, at the rate of seventy beats a minute. It is our task as physicians to supply the intelligence it does not possess and to apply the control as soon as we perceive the heart to be constantly or persistently taking more beats than are economic in the performance of its work.

Sustained tachycardia is a feature that should always rouse our curiosity for the earlier we intervene, where this is possible, the less is the curtailment of the diastolic period and all that that entails. An analytical attitude to all increases in rate is therefore essential in all true clinicians. Distinction between the tachycardia which is compensatory to a loss in myocardial force and that which results from extra-cardiac demands must be made in all cases. Time will not permit full consideration of the intrinsic and extrinsic or essential



and non-essential tachycardias, but I should like to direct your attention to a simple test from which we can obtain considerable assistance in distinguishing the nature of the tachycardia. It consists of withdrawing the respiratory aid to the return of blood to the heart. The tendency to create negative pressure in the thorax by the descent of the diaphragm in respiration is a definite factor in the filling of the right heart. If we eliminate this element by inducing apnœa we throw an additional load on the heart. Where, in presence of deficiency in myocardial force the circulation is only maintained symptom-free by a compensatory increase in rate, any additional cardiac load will be carried by augmenting the number of contractions still further. By inducing apnœa such an additional cardiac load comes into being. An increase in rate as a result of the apnœa test should always excite suspicion of loss of myocardial force in the absence of increased metabolic rate.

Infinitely more common is the extrinsic tachycardia and two groups may be recognised, and in both the cause of the increase in rate is preponderance of the sympathetic. Where this sympathetic excess is not accompanied by any marked increase in metabolism (such as occurs in Graves's disease and in febrile states) the induction of apnœa usually produces a pronounced slowing action through the vagus. Thus psychic stimuli and inco-ordination in the autonomic system which readily give rise to tachycardia can be eliminated by the apnœa test and by so doing the sympathetic activity can be recognised as non-essential in origin. Where the metabolic rate is markedly increased the stimulation of the sympathetic is usually too strong to be dismissed by so mild an excitation of vagus as can be induced by apnœa and in varying degrees the tachycardia is untouched. I commend to you the apnœa test as an aid to discerning the early case which is heading for failure through loss of coronary efficiency from shortening of diastole.

#### BASAL SLEEP

Rate and force being reciprocals in the work of the heart, a true reflection of the efficiency with which the myocardium is carrying its load is to be found in the rate when the metabolism is at its lowest. The metabolism is basal only in sound sleep between the hours of 2 and 4 in the morning. The rate under such conditions informs us truly of the ease with which the myocardium is maintaining the circulation. Certain conditions, however, must obtain.

- (1) Sleep must be sound and undisturbed by excitement of dreams.
- (2) No food should have been taken for four to six hours previously.
- (3) No overheating by excessive bed-clothing or room temperature should be permitted.
- (4) Quietness must prevail for the ears never sleep and sound can increase the heart rate without otherwise disturbing consciousness.

Needless to say, there must be no pyrexia.

Given such conditions with careful and gentle pulse-taking the rate will provide the best guide to assessing myocardial efficiency. It is not possible to state precise figures for the inherent or personal factor varies with each heart. But it may be said that a truly basal sleep rate of over eighty should lead one to suspect a loss in myocardial force or increased metabolism.

The reason why greater use has not been made of the basal sleep rate in clinical medicine is to be found in the awkwardness of the hours of observation which almost preclude its use in general practice. In hospital practice it is much neglected and with less reason. I commend it to you. It is of great value in suspected hypermetabolism from any cause and in convalescence it is the best guide to presence or absence of cardiac debility for it informs us of the number of beats required to meet basal conditions and this directly reflects the force of the myocardium when the heart is doing no more than maintain the essential minimum in circulation.

Whenever the results are surprising, further enquiry is indicated.

### THE ARRHYTHMIAS

Now let us look at diastole in the arrhythmias. We may venture to say that the immediate prognosis of any heart contracting irregularly depends not on the irregularity in contraction but upon the degree of disturbance of the duration of diastole over a period of time. If the total diastole of the day is not much altered in either direction cardiac efficiency will not be gravely affected. We are, of course, here speaking of the heart's capacity to meet its daily obligations and not of the etiological factor giving rise to the arrhythmia. Thus sinus arrhythmia, occasional extra systoles, and asystoles, are innocent features *quæ* cardiac efficiency. As regards auricular fibrillation, which as you know may last years with little disability, what decides whether a patient suffering from this disorder will walk in or be conveyed on a stretcher to the clinic is decided entirely by the degree of interference with diastole. Where diastole is seriously curtailed by the rapidity of the ventricular contractions over a period of time congestive failure will be present. Where the ventricular rate is not much disturbed there will be no symptoms. Indeed, many instances of slow fibrillation are found incidentally in consultation for non-cardiac disorders. (In such ignorance the bliss should not be disturbed.)

Your clinical experience will, I venture to think, confirm this generalisation—that arrhythmias which do not profoundly change diastole in either direction—shortening or lengthening—carry no danger of cardiac failure. The proof of this statement is to be found in the arrhythmias which do not fall into this category, namely, flutter, paroxysmal tachycardia and heart block. In each of these diastole is altered beyond the physiological range and the prognosis depends upon the time element in restoration of an adequate diastole. In

extreme degrees of tachycardia the coronary deficiency is only a matter of time. Frequently conduction of impulses from the auricles to the ventricles becomes impossible and the myocardium is rescued by the appearance of heart block (either complete or incomplete) or auricular fibrillation and this change reduces the ventricular rate and provides the myocardium with breathing space between beats during which the coronary flow attends to things it has left undone. Indeed, the myocardium may so quickly recover that after a short period the ventricles again aspire to keep pace with the exuberant auricles only to fall back in disorder once more; a procedure which may repeat itself over and over again.

No more eloquent testimony of the importance of diastole is to be found than in these cases of the game but foolish heart. In such cases no one has any doubt about the objective in treatment. Reduction of the ventricular rate is a matter of urgency. Remove the dramatic element and spread this same disorganisation of the coronary flow over weeks instead of hours and we have the common case of pre-failure tachycardia which is so often neglected.

### HEART FAILURE

Now let us go a step further and consider briefly the problem of heart failure. Certain features stand out. In congestive heart failure there is usually some degree of tachycardia and the first indication of this type of failure in most cases is an increase in rate as a compensation to a fall in stroke-volume of the ventricles. This tachycardia always carries with it the hope of recovery for in it is an element of youth and there is much good in a myocardium that can make the rate carry the circulatory load when force has declined. This is the reciprocal action in the normal heart. The route usually traversed by a heart in distress is to contract oftener to make up the deficit in force. When the compensation is sustained too long then do we see the vicious effect of curtailed diastole with diminished total coronary flow. Under these conditions the classical picture of congestive heart failure is not long delayed. In this form of failure, the symptoms are precipitated by the uneconomic method adopted by the heart to meet the circulatory calls. Regardless of its own metabolic needs the myocardium responds to the sympathetic demands from all organs. It runs faster on less rations and unless some power intervenes to restore diastole, coronary insufficiency will bring the heart to a standstill. Recognition of this pre-failure tachycardia can very materially alter the cardiac outlook. Even in gross failure with tachycardia there is always hope, for in the digitalis series we have a powerful vagus stimulant with the faculty of depressing the vital activity at the SA and AV nodes which then respond only to the stronger stimuli. Thus is diastole restored.

Conversely, where force fails despite an adequate diastole the

outlook is indeed grave from the onset. In such cases failure arises because the myocardium is incapable of tachycardia—the normal reciprocals of rate and force are no longer operative. In those cases that survive one may postulate the presence of gross morbid change in either the myocardium itself or in the coronary vessels. For these unfortunates we can do little beyond reducing the cardiac load by every means at our disposal and by raising the quality of the metabolites and blood where there are such indications.

Finally there remains to be considered the cardiac state when diastole is unduly prolonged. It has long been recognised by life insurance associations that in moderate degrees of inherent bradycardia the expectancy of life is greater than usual. Why this is so will be readily appreciated.

Diastole over-night is a subject which probably has not kept you awake. Indeed, I doubt whether you have given it a thought and quite rightly for you are not at the age when it could play any important rôle in your life.

As you well know, the heart slows down over-night under the influence of the vagus. Thus is diastole prolonged. In youth this is of inestimable benefit but in your second youth or childhood it may hold other possibilities.

Along with the slowing of the pulse over-night the blood pressure also falls. I need not dilate upon the possibilities when both are excessive or exaggerated. And if we add arteriosclerosis we have a triad which accounts for no small incidence of those emergencies of the night in thromboses, both cerebral and coronary. The danger is greatest at the period of lowest metabolism, between the hours of 2 and 4 in the morning, when the vagus is in undisputed charge of the economy. The rôle of diastole in any such nocturnal disasters is purely passive—the greater the vagal control the longer the diastole and the greater the chance of standstill of the blood in the finer vessels. Where coronary occlusion has already occurred, nocturnal bradycardia invites further thrombosis and this we see in those victims of coronary occlusion who survive the initial disaster only to succumb when the pyrexia associated with the lesion subsides and nocturnal diastole is again prolonged. Any measure to prevent the vagus from assuming full control under such circumstances is sound practice. Indeed, it may be life-saving.

Prolongation of diastole is also a factor in many cases of so-called cardiac asthma and it is a feature in vagotonia. So strong may be the vagal influence on the heart over-night that it may persist despite the fact that another day has dawned and motor activity has been resumed. It is quite within possibility for a person to get out of bed with his heart still soundly asleep. In its most innocent form it is found in those persons who take the heart by surprise by jumping out of bed, and after a few strides find themselves on the floor—the circulation of the room unfortunately taking precedence before the

blood. On subsequent days they rise wiser and with meditation. Insurance statistics in the U.S.A. record an inordinate incidence of sudden deaths in the lavatory over-night. There is little doubt that this site of election, as the surgeons say, is occasioned by nocturia and that the cause is a sleeping heart and a dormant blood pressure.

With the dangers of the night behind them, vagotonics, with their low blood pressure and slow hearts, face the forenoon with no great enthusiasm. Many confess to be feeling half alive before lunch and only come to life in the evening. Lack of energy and giddiness does much to induce a loss of confidence in themselves and it is important that they should be informed of the cause of their discomfort before depression takes them round the corner to the psychiatric world. It must be confessed that bradycardia in this syndrome plays a rôle secondary to the low blood pressure; the object of treatment, however, is clear—to counteract the action of the vagus. The problem can be approached from two opposite roads—depression of the vagus and/or stimulation of the sympathetic—or in simple terms raise the metabolism. The approach depends upon the case.

Where over-night vagal influence is a potential factor for mischief, *e.g.* after or in threatened thromboses, cerebral or coronar *thrombosis*, and cardiac asthma or Cheyne-Stokes breathing, the metabolism should not be allowed to become basal. A night-cap of whisky has *its origin* in its physiological response in raising the metabolism—a somewhat condoning and consoling thought. Gentle awakening to repeat the dose after four hours where thrombosis has recently occurred is more than justified; then the stimulant should be warm and of easy access at the bedside in a thermos. Thyroid an hour or so before sleep has many advocates. Adrenalin solution as a direct sympathetic stimulant is somewhat fleeting in its action but as a solvent for atropin (Gr. 1/100) a vagal inhibitor and strychnine (Gr. 1/100) a central stimulant it is of decided value and in urgent cases may be repeated four-hourly for some days. For simple vagotonia, with forenoons governed by disinclinations and inertia, vagal dismissal by belladonna, caffeine and benzedrine can bring much relief and restore confidence. Let me also add that the waking headaches in arterio-sclerotics from nocturnal hypometabolism respond also to these measures and for this relief patients are profoundly grateful. Ephedrine with the morning tea and a Bellergeral tablet after breakfast I have found most effective in these elderly subjects.

In conclusion allow me briefly to restate the case for diastole. Diastole is no negative phase. Diastole is by far the more important phase in the cardiac cycle. Diastole decides the welfare of the myocardium itself. The coronary circulation functions almost exclusively in diastole and systole reflects directly the adequacy of the diastolic phase. Systole looks after the general systems, diastole looks after the heart. The heart rate is the clinical sign beyond all others of the state of the myocardium, and under basal conditions

it is the only assessor of the force of the myocardium that we possess to-day in clinical medicine. Let us never forget that the heart possesses no discrimination as to the importance of the demands made upon it and in its response it displays no vestige of economy either general or myocardial. The myocardium in fact possesses strong suicidal tendencies necessitating at times sedatives in the form of digitalis. Its prodigality is sustained only by the generous endowment in reserve power. But the day comes when it finds itself falling short. Before that day, and after, it is our purpose as physicians to conserve its inheritance. We can do no better than grant to it adequate diastole in which the coronary circulation has the element of time necessary to restore to the myocardium its ease in function.

I trust you will now proceed to cast a suspicious and analytic eye on tachycardia whenever it is met.

## REMARKS ON THE OBSTETRICAL MANAGEMENT OF THE PREGNANT TUBERCULOUS PATIENT

By W. C. ARMSTRONG, M.B., F.R.F.P.S.(G.), F.R.C.O.G.

Consultant Obstetrician, Robroyston Hospital, Glasgow

I CONSIDER it a great privilege to have been given this opportunity of participating in the discussion on the subject of the tuberculous gravid patient, or perhaps the subject might be more aptly designated the accident of pregnancy in the patient suffering from pulmonary tuberculosis. I must confess that I have always been interested in this study. Consequently, when, some three years ago, I was fortunate to have the opportunity to investigate the problem at first hand, with the full collaboration of the chest physician and the pædiatrician, I was very pleased indeed to take charge of the obstetrical side of the problem.

Dr McIntyre has dealt with the more important medical aspects of the problem, and it is now my privilege to deal with the subject from the obstetrical point of view. In all honesty I must admit that specific obstetric problems were seldom encountered. Labours, in general, were unaffected, except in one series of cases which were suffering from advanced lung lesions, *where it was noted that labour was notably short and comparatively easy*. Under the circumstances you will agree that this was fortunate. The same phenomenon is noticeable in cases with a marked cardiac lesion and various authors have commented on this fact. To date, and contrary to reports by others in this series with one exception, no deaths occurred during labour or immediately after labour in these seriously ill patients. One death was recorded, however, after delivery. The patient in question, suffering from bilateral apical tuberculosis, quiescent in type, was admitted to the obstetric unit in labour and gravely ill with severe vaginal hæmorrhage. A blood transfusion was commenced along with the usual shock therapy and the patient being fully dilated a forceps delivery was carried out, but, despite the rapid arrest of hæmorrhage, the patient was so exsanguinated and shocked that she died. Autopsy added little to our knowledge, no opinion being given on the precise cause of death.

*Toxæmias*.—Toxæmia of pregnancy was uncommon; 5 instances of albuminuria and high blood pressure and one of eclampsia were recorded. Except for one in which the lung lesion was quiescent, the pulmonary condition in each instance was arrested. It is interesting to note that, to date, no patient with active phthisis has suffered from a late toxæmia of pregnancy.

Read at a meeting of the Tuberculosis Society of Scotland, October 1949.

*Therapeutic Abortion.*—While the place of therapeutic abortion and termination of pregnancy is extremely difficult to define, being dependent as it is on so many and varied factors, such as parity, sociological problems, and the patient's general physical and mental condition, in Robroyston Hospital the procedure has been reserved, generally, for those suffering from an active bilateral pulmonary lesion considered to be unsuitable for collapse-therapy, and in whom the prognosis is usually universally bad. Attention is drawn to a comparison between cases suffering from a bilateral lesion who went to term and those in which, suffering from a similar lesion, pregnancy was terminated. Twenty-eight per cent. of the former group and 25 per cent. of the latter group deteriorated. This comparison would appear to indicate that pregnancy has an adverse effect on the tuberculosis. On the other hand, it cannot be said that the procuring of therapeutic abortion necessarily guarantees cure. Since the former group were seen for the first time late in pregnancy and for the most part had received little or no ante-natal care, this result, although unfortunate, is not altogether surprising. It is interesting to note that none of the 23 patients suffering from quiescent, arrested or recovered lesions and who were pregnant for the second time during the period under review deteriorated. It would seem, therefore, that once a lesion is healed or stabilised pregnancy has little or no adverse effect. *In addition, it might perhaps be reasonable to infer from these repeated pregnancies after such a short interval that the tuberculous patient has an increased fertility.*

*Management of Labour.*—In connection with the actual management of these patients an endeavour is made to make delivery as easy as possible. Analgesics and sedatives are given where necessary, and all resources are employed to prevent prolongation of the second stage of labour. Where delay in labour is evident or anticipated, forceps are applied at the earliest possible time, after preliminary episiotomy, the object being to reduce the second stage to the minimum, preventing thereby the "pressing down" of this stage being unduly protracted or distressing.

*Anæsthesia.*—While choice of anæsthesia is generally covered by custom, in Robroyston Hospital, preference is given to spinal anæsthesia. The inhalants, ether and chloroform, are avoided because of irritating effect to the respiratory tract. In some instances, particularly in the "bad risk" type of case, local pudendal block anæsthesia has been employed.

*Termination of Pregnancy.*—The technique of termination of pregnancy is of interest. I much prefer the abdominal hysterotomy, and as a rule, perform this operation in all cases later than two and a half months. Vaginal delivery after this latter period is not without the presiding risk of local trauma, hæmorrhage and sepsis. If necessary, the abdominal operation can be performed under local anæsthesia.

*Management of the Child.*—Concerning the child at term it will



have been gathered from Dr McIntyre, that the majority are normal, well-nourished babies, congenital tuberculosis being exceedingly rare. While this may be so, routinely, cord blood is sent to the laboratory for a direct smear and culture on Loewenstein medium and all suspicious looking placentæ are sent for pathological examination. To date, no tubercle bacilli have been found in either type of specimen. As far as the feeding of the infant is concerned, breast feeding is permitted only in exceptional circumstances, *i.e.* arrested or recovered cases. All mothers are required to wear masks. For those who are specially interested in this aspect of the problem, an investigation to detect the presence of the tubercle bacillus in the breast milk has been carried out in Robroyston. Milk expressed on 3rd, 5th, 7th, 10th and 21st days of the puerperium has been examined bacteriologically and biologically. As yet, *tubercle bacilli have not been isolated in the specimens collected.*

On the question of prophylactic vaccination of these children, I consider, and I hope you will agree with me, that such immunisation is long overdue.

To my mind, segregation of the children, especially in a nursery and under the surveillance of a competent pædiatrician, will serve a threefold purpose. Thus, not only will they stand to benefit from vaccination but good health, so often precarious in the neo-natal period, especially in the home, will tend to be ensured, while in addition the mother herself will reap the reward of an 8 to 12 weeks' valuable and much needed rest.

In conclusion, I would like to express my thanks to Dr Foulis, Physician Superintendent, Robroyston Hospital, for his helpful advice and administrative ability in this work. In addition, I consider myself fortunate in having the opportunity and privilege of collaborating in this investigation at Robroyston Hospital with Dr J. P. McIntyre.

# GENERAL OBSERVATIONS ON PREGNANCY AND TUBERCULOSIS WITH SPECIAL REFERENCE TO COLLAPSE THERAPY

By J. P. MCINTYRE, M.D.

Consultant Chest Physician, Robroyston Hospital, Glasgow

BEING conscious of the complexities of the problem of pregnancy and tuberculosis and aware that many of mature experience now present have made this subject their special study, it is naturally not without much diffidence that I open this discussion. To justify myself, it can be said that in Robroyston Hospital I have had unusual opportunities of putting into practice the improved precepts of preventive medicine, tuberculosis and obstetrics, and recently have given much care and consideration to the problem under discussion. Furthermore, I hope to add to my knowledge of this intriguing subject from the comments and deliberations of my colleagues following this address, a fact which, as much as any, influenced me in deciding to read this paper to-day.

Unfortunately, the limitation of time makes it impracticable for me to survey this wide field completely, compelling me to restrict my observations to certain general principles governing the management of the pregnant tuberculous patients in Robroyston Hospital, and to an outline of available facilities there for these patients. Finally, with special reference to collapse therapy, I will endeavour to evaluate these therapeutic principles as applied during pregnancy and for a period of two to three months following delivery.

Few problems in clinical medicine have provoked more controversy than that of pregnancy and tuberculosis: although the subject of an immense literature, conclusions are incomplete, and opinions are of wide extremes. Thus, on the one hand, authorities represented by Rist (1921), Norris and Landis (1918), firmly believe that pregnancy has an adverse effect on tuberculosis, especially its active forms, and, holding no brief for conservative therapy, they advocated abortion. Such a view, however, is unacceptable to others, who hold the preponderant opinion that the effects of pregnancy on tuberculosis are innocuous and sometimes beneficial.

According to modern concepts, however, the general trend is now one of compromise. While the danger of the combined conditions are not categorically denied or minimised, much medical evidence can be adduced to show that under ideal environmental conditions, with appropriate and adequate nursing and medical attention during gestation and the immediate postpartum period, conception occurring in the course of pulmonary tuberculosis need not necessary spell doom.

Read at a meeting of the Tuberculosis Society of Scotland, October 1949.

For this modern approach to the problem credit is due to Hill (1928), Ornstein and Kovnat (1935), Barnes and Barnes (1930) in America, Forssner (1924) in Scandinavia, Oxenham (1941), in Australia, and nearer home, Cohen (1946), Marshall (1931), Simmonds *et al.* (1947) and Brooks (1940). According to these workers the character of the lung lesion rather than the pregnancy is the deciding factor in prognosis. Coincidental with this growing tendency to recognise the separate elements of the combined conditions, the scope and the application of collapse therapy has increased and its value as a potent public health measure been enhanced. Moreover, with the realisation that the ultimate prognosis in tuberculosis is influenced by factors not exclusively medical, choice of treatment to be adopted will depend on taking such factors into account in every individual case. Consequently, in Robroyston Hospital, attempts are made to treat the patient, her disease and her pregnancy against the broad background of personal, social and environmental conditions. Consideration is given therefore, to (1) family history, (2) previous sanatorium treatment, (3) character and extent of the existing lung lesions, (4) obstetrical history, past and present, with particular reference to the reaction of the patient to her present pregnancy, (5) factors difficult to codify, but which are nevertheless common to the joint conditions, namely, socio-economic circumstances and individual nutritional states.

### THE TUBERCULOSIS MATERNITY UNIT

Before passing to a discussion of the results of treatment, it is pertinent at this point to describe in some detail the organisation in Robroyston Hospital which, in my opinion, constitutes the foundation essential for effective treatment.

It was in January 1947, that the Local Authority, City of Glasgow, first made provision in the Maternity Unit, associated ante-natal and post-natal clinics, Robroyston Hospital, for all expectant and nursing tuberculous mothers, resident within the city. To meet all contingencies, obstetrical and medical, the staff included a consultant obstetrician and physician, while responsibility for the child after delivery devolved upon the pædiatrician to the hospital. In the first instance patients are referred, with records, to the ante-natal clinic in the hospital, from the tuberculosis dispensaries and welfare clinics throughout the city. Following routine examination, a combined assessment is made jointly by both medical advisers, in attendance, at the ante-natal clinic. While it is difficult to classify tuberculous lesions satisfactorily, for practical purposes the following scale of assessment, based on clinical, radiological and bacteriological examination, is employed :—

- (1) Quiescent cases in which the general condition of the patient is good, toxæmia is absent, tubercle bacilli are not present in the sputum, and serial X-rays reveal no evidence of pulmonary progression of disease.

- (2) Arrested cases, in which the disease has been quiescent over a continuous period of two years.
- (3) Recovered cases, in which the state of quiescence continues uninterrupted for five years.
- (4) Active cases, discharging tubercle bacilli in the sputum during the preceding three months.

Recognising the serious potentialities of pulmonary tuberculosis and pregnancy and the importance therefore of a careful "follow-up" investigation, the mothers are advised to report two to three months after delivery to the post-natal clinic for examination. Those with an established pneumothorax, however, report at weekly intervals for refills.

Furthermore, arrangements have been made for the infants to be examined twice every three months in the first year of life, every six months in the second, and yearly thereafter. A first visit to the Infant Consultation Clinic includes not only a Mantoux Test, but a thorough clinical examination. The Mantoux Test is read after an interval of 48 hours and the result is recorded: positive reactors have a chest X-ray examination. Doubtless in the near future B.C.G. vaccination will be available for the unequivocal negative reactor. Comprising as it does, its own ante-natal and post-natal department, maternity ward with separate labour room, nursery, isolation and ante-natal ward, this Maternity Unit is, I believe, one of the few of its kind, to date, in Great Britain.

#### SUMMARY OF CASE RECORDS

During the period January 1947 to July 1949, 350 pregnant tuberculous patients were admitted: 208 were primiparæ, 142 multiparæ. Three hundred and twenty-two completed full-term pregnancies. Twenty-one were pregnant for the second time, while two were pregnant for the third time in the period under observation. In 23 patients, the pregnancy was terminated surgically. Five patients died undelivered, sixteen patients were untraced two to three months after their confinements. All patients admitted had adult phthisis, 119 being classified "active," 154 "quiescent," 51 "arrested" and 26 "recovered." Distribution of the lung lesion was predominantly unilateral in 175 patients, while in 91 a slight contralateral lesion was present in addition: 84 patients had bilateral pulmonary tuberculosis. Since no selection was made for the purpose of admission, results obtained from treatment may be regarded as applying to all types of tuberculous lung lesions associated with pregnancy. Surgical measures employed, to date, in Robroyston Hospital in the treatment of the pregnant tuberculous woman include (1) phrenic nerve interruption, (2) phrenic nerve interruption plus pneumoperitoneum, (3) artificial pneumothorax, (4) artificial pneumothorax plus internal pneumonolysis, (5) thoracoplasty.

As a rule pregnancies were permitted to proceed to term in (1) confirmed, arrested, quiescent and recovered lesions; (2) those in which pregnancy supervened during pneumothorax therapy, provided available evidence showed the effectiveness of such treatment; (3) pregnancies advanced more than five months, irrespective of the lung lesion. In certain "borderline" cases, where seen early enough, the decision to continue the pregnancy was postponed for a month or so, during which time the patient continued to be under observation, and further attempts were made to assess with greater accuracy the status of the underlying lung lesion.

Further scanning of the records revealed that, in 72 instances, demonstrable lung lesions were discovered for the first time during pregnancy, 67 of which were active in character. In all, 58 patients received collapse therapy, including 25 pneumothoraces, 20 of which were equally divided between the second and third trimester, the remaining five being induced during the puerperium. Twenty-five patients received phrenic nerve interruption, 2 of which were performed during the first trimester, 5 in the second and 9 in the third. Of the remaining 9 patients, 6 received pneumoperitoneum, in addition to phrenic nerve interruption during the immediate post-partum period. Finally, 7 thoracoplasties were done, 4 during and 3 after pregnancy.

### RESULTS OF TREATMENT

It is recognised that conditions of pregnancy and tuberculosis with their diverse symptomatology and course, do not lend themselves to providing reliable statistics on which to base final judgment. Nevertheless, certain definite conclusions can be drawn from a number of significant observations of practical importance which emerged from this study. In the first instance the compatibility of pregnancy and collapse therapy, even thoracoplasty in certain selected instances, was manifest. Despite the apparent decrease in the total lung volume resulting from the disease, the collapse therapy superimposed and the pregnancy itself, marked dyspnoea was not a prominent symptom, except in two isolated instances in which the pneumothorax was complicated by the presence of an effusion. It is the opinion of the writer, based on experience, that fear of incapacitating respiratory embarrassment is largely unfounded. Accordingly, *per se*, it should not warrant therapeutic interruption. Jameson (1935), in America, however, does not subscribe to this view, especially when thoracoplasty is under consideration. From observations based on 11 thoracoplasty case reports, he concluded that dyspnoea during delivery in these patients was a very real danger. Indeed, it was more to be feared than exacerbation of the underlying lung lesion. While the results of this investigation, to date, do not substantiate this claim, nevertheless, as a precautionary measure, attempts should be made to eliminate pre-operatively the potentially dyspnoeic patient, particularly when

such a formidable procedure as thoracoplasty is under consideration. Concerning pneumothorax complicated by pregnancy, progression towards effective pulmonary relaxation should be under constant fluoroscopic control for, ironically, danger results, in the author's opinion, not so much from dyspnoea as from inadvertent and premature loss of pneumothorax, the result of failure to recognise the fundamental that associated with pregnancy the rate of absorption of air from the pleural space may be greatly increased. It is interesting to note that only one patient out of a total of 21 treated by collapse therapy early in pregnancy showed slight evidence of deterioration, while under observation. By comparison, 3 out of a total of 19 who received collapse therapy late in pregnancy died. While many complex factors combine to render the explanation of results in this present problem difficult, albeit the impression was formed that this unfavourable result was not unrelated to the time at which the collapse therapy was administered. It is not inconceivable that if the pregnancy and the tuberculosis in this latter group had been treated concurrently and adequately, early in the ante-natal period, the result might have been quite different. The time at which the tuberculosis receives treatment being of obvious signal importance, the logical conclusion is inevitably reached that chest X-ray survey should be taken routinely in all ante-natal clinics throughout the country. If this principle was applied, not only would the lesion be observed at an early stage in its evolution, when it is more likely to respond to appropriate treatment, but the period of watching and waiting, which is so desirable, but often impracticable because of the pregnancy, would be available.

Several noteworthy features emerged from consideration of these patients in whom the tuberculosis antedated the pregnancy. In all 278 received routine sanatorium treatment prior to conception; of these, 125 had received pneumothorax therapy, 7 phrenic nerve interruption, 5 phrenic nerve interruption plus pneumoperitoneum, and 25 thoracoplasty. Twenty-three patients had established pneumothoraces at the time pregnancy supervened. Significantly, the prognosis was found to be much better in this larger series of patients. Of this group only 8 died. This comparatively low mortality figure was attributed to several factors, chief of which was the nature of the lung lesion at the time of conception, the majority being quiescent, arrested, or recovered. As known tuberculous patients and still under the care of the chest physician, there is no doubt that they received appropriate and prompt medical attention for their chest conditions at an early stage in their pregnancy.

*The effect of the pulmonary lesion on the infants was negligible.* Three hundred and forty-nine infants were born to 322 mothers, 320 being full time with deaths in 6. In addition, 2 infants died shortly after birth from congenital causes. Deaths in the neo-natal period include one from pulmonary tuberculosis confirmed by autopsy, 2 from tuberculous meningitis, and 5 from gastro-enteritis. Seventeen out of

a total of 21 premature infants died. Thus, with the exception of prematurity, the figures from neo-natal deaths were not very high.

### CONCLUSIONS

Despite our present-day regrettable ignorance of many of the fundamentals associated with this problem, on the basis of this investigation certain generalisations are permissible. While the adverse effects of pregnancy and pulmonary tuberculosis, especially its active form, can not be categorically denied, nevertheless, as shown, these effects are capable of being modified appreciably. Moreover, it is submitted that with the prompt application of modern methods of treatment for the tuberculosis, the closer and more harmonious co-operation between patient, accoucheur and the specialist in tuberculosis, finite assessment of this problem might one day be forthcoming. Reviewed as a whole, stress must be laid on prophylaxis, early diagnosis and treatment including plans for the after-care of the patient. From the prophylactic point of view, recommendation in favour of conception is best withheld until the lung lesion has been arrested three years. With reference to diagnosis, *the extreme importance of early recognition of an existing lesion can not be over-emphasised*. So-called "doubtful" cases encountered at ante-natal clinics should be examined by the tuberculosis physician to confirm or deny the existence of pulmonary disease. For the proved lesion, collapse therapy applied timely and wisely is the mainstay in the management of the pregnant tuberculous patient and may save not only the mother but the child as well. Finally, it should not be necessary to stress the importance of a comprehensive after-care scheme incorporating assistance, financial or in kind.

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## OBITUARY

JOHN ORR, M.D., F.R.C.P.E.

DR JOHN ORR died in the Royal Infirmary of Edinburgh on 28th November 1949, after a short illness.

His life was a very full one for he had varied gifts and abilities not one of which rusted in him unused.

I met him for the first time in Calcutta in 1934. He was then visiting, on his own initiative, the medical schools and institutions of India, enlarging his experience and knowledge of medical education and administration. As I was then myself actively engaged in teaching and administration, it was a great pleasure to meet and talk over these important matters with one so experienced and knowledgeable. When I returned to Edinburgh in 1935 as Medical Superintendent of the Royal Infirmary I was delighted to find Dr Orr one of the Managers and for the next fifteen years I enjoyed the pleasure of intimate personal fellowship with one who, alike in professional and outside interests, was keen, alert and enthusiastic and who could communicate his enthusiasm and interest to others.

His great life's interest was his profession. He was a well trained and experienced, logical and disciplined physician, expert and shrewd, definite in diagnosis and in the practical application of his knowledge. Having studied and thought over a case, he had then surety in his diagnosis and high confidence in his treatment. This confidence he was able to communicate to his patient, a great gift in any doctor.

After his retiral from practice about twenty years ago his main interests were in the School of Medicine of the Royal Colleges and in the Royal Infirmary. He took over the Deanship of the School at no easy time. His belief in the School's worth, his hard work and confidence, and sympathetic administration successfully carried on the School until he was able to hand it over to an able successor.

He served as a Manager of the Royal Infirmary for over twenty years and every year was one of increasing interest and service. I have personally to thank him for much help and guidance willingly given. He quickly grasped the essentials of any problem and was sure to discover a likely solution. The Infirmary owes him a particular debt for his work as Convener of the Radiological Committee. He studied the various problems of the Department until he had an intimate, clear and detailed knowledge of its present and future needs in equipment and staff. He was able by his logical and forceful and persuasive presentation of his problems to carry his schemes through committee and the Board with unusual speed and celerity. He was a shining example of what the voluntary principle could achieve given interest and enthusiasm in its Board members.

But he got much enjoyment from the exercise of his gifts in directions other than medical. Chief, perhaps, was his interest in music. He had a high appreciation of good music; he had a good bass voice and entertained many a company with his singing of Scots songs. He was a Director of the Edinburgh Concert Society and for many years was its Chairman. His business acumen



and talent for negotiation bore good fruit here, and concert-goers in Edinburgh have much to thank him for. At the concert of the Scottish Orchestra on 8th December 1949 the large audience paid thankful tribute to his work and his memory, while the orchestra played Elgar's noble Nimrod Enigma Variations.

He was a Watson's boy and kept up his affection for the College to the end, serving two terms of office as President of the Watsonian Club. He was a keen and expert bowler, and skipped many a winning team in club and international games. He loved Scotland and knew it well, especially the Highland country in and around Speyside. A cultured student of literature, in conversation and speech he could quote readily and aptly from his wide store and knowledge of English and classical literature.

But those who knew John Orr intimately and shared his friendship will remember him more for his personal qualities. He was by nature cheerful and kindly, understanding and sympathetic and ever ready to help not only with advice but with real practical help—Christian virtues these might be called, and rightly so. Throughout his life these were reinforced by his simple religious faith, practised quietly and serenely and confidently, and never with ostentation.

His going is a loss but his memory and influence remain. A fine life well lived.

A. D. S.

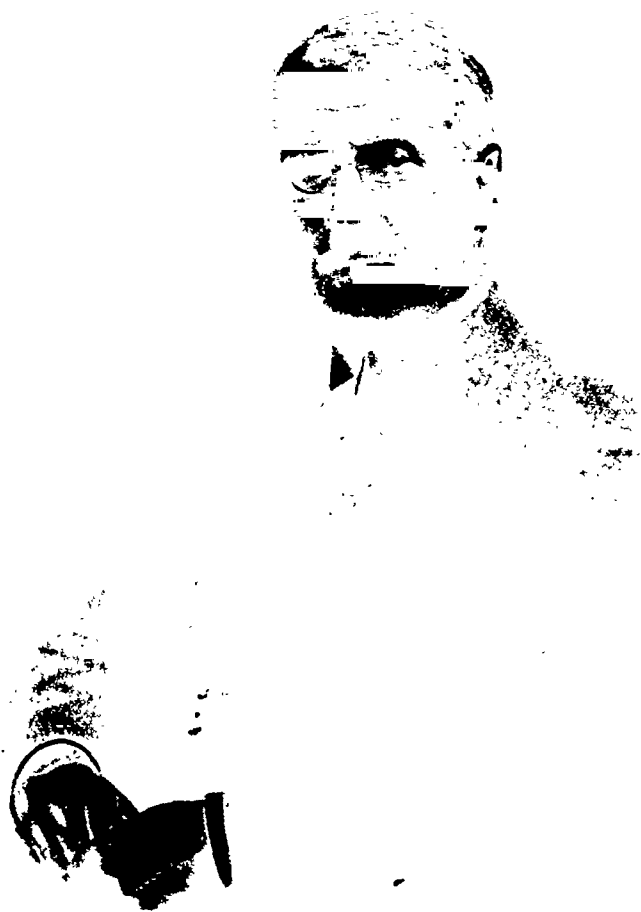
John Orr, born in Edinburgh on 5th September 1870, was the son of Samuel Kely Orr, a business man. Educated at George Watson's College and at Edinburgh University, he graduated M.B., C.M. with honours in 1891 and the same year qualified M.R.C.S., L.R.C.P.Lond. In the winter of 1891-2 he acted as resident physician to Sir James Affleck and later was resident at Chalmers Hospital and at the Simpson Memorial Hospital. Joining the Royal Medical Society in 1891 he was elected Senior President in 1894. He became a member of the Royal College of Physicians in 1894 and two years later proceeded to the Fellowship and took the M.D.

Attracted to general practice, John Orr became first an assistant in Edinburgh and then a successful principal. His special flair for teaching found outlet as physician to the Western Dispensary and later as lecturer in *Materia Medica* in the School of the Royal Colleges.

From 1924 to 1945 Dr Orr acted as Dean of the extra-mural school and during his term of office made trips to India, Canada and the United States to study problems of medical education. He served on the Council of the Royal College of Physicians from 1926 to 1930 and as representative of the College on the Board of Management for the Triple Qualification for many years. From 1926 until the introduction of the Health Service he was a member of the Board of Managers of the Royal Infirmary, an office which gave ample scope for his special qualities of mind and body.

In spite of his 80 years, Dr Orr remained active and vigorous and almost to the end of his last illness continued to look forward to further activities.

To his widow and family we extend our deepest sympathy.



*Photo by*

JOHN ORR

*E. R. Yerbury*



## NEW BOOKS

*Textbook of Ophthalmology*. Vol. IV. By Sir W. STEWART DUKE-ELDER. Pp. 4627, with 79 tables, 3985 illustrations and 73 plates. London: Henry Kimpton. 1949. Price 70s.

The advent of the fourth volume of Sir W. Stewart Duke-Elder's *Textbook of Ophthalmology*, delayed as it was by six years of war service, is welcome to all ophthalmologists. Those who have looked forward to its production will not be disappointed. It deals with the neurology of vision and motor and optical anomalies. These are dealt with in a most comprehensive and orderly way and in every particular this latest arrival reaches the previous very high standard. Not only is the *Textbook of Ophthalmology* of the greatest service to ophthalmologists throughout the world but is of inestimable value to the teachers in this subject as a complete and reliable work of reference.

*Modern Practice in Ophthalmology*. Edited by H. B. STALLARD, M.B.E., M.A., M.D., F.R.C.S. Pp. 523, with 231 illustrations and 30 colour plates. London: Butterworth & Co. (Publishers) Ltd. 1949. Price 65s. net.

This newcomer to the Modern Practice series has been edited by Mr H. B. Stallard who has himself written several chapters. All the contributors are well-known ophthalmologists. Individually, therefore, as would be expected, the separate chapters are excellently written. There is on some occasions a tendency to overlap so that the same conditions are discussed in different sections by separate authors. The book is lavishly illustrated and the diagrams well annotated. One can have no hesitation in recommending it to the practitioner who wishes to have a fuller understanding of the ophthalmological problems which must periodically crop up in practice.

*Ophthalmic Medicine*. By JAMES HAMILTON DOGGART. Pp. 329, with 87 illustrations and 28 colour plates. London: J. & A. Churchill Ltd. 1949. Price 32s.

As is stated in the preface "the main object of the volume is to emphasise how intimately the eye is linked not only with adjacent structures but also with remote parts of the body." As would be expected only the medical aspect of ophthalmology is dealt with and surgical and therapeutic details are omitted. There is much good material in this book and it is up to date in its exposition of the many medical conditions and syndromes dealt with in its thirty-five chapters. It is a very easily read volume and is well illustrated.

*Aviation Medicine*. By K. G. BERGIN. Pp. xiv+447, with 131 illustrations. Bristol: John Wright & Sons Ltd. 1949. Price 35s. net.

With the increasing popularity of air travel some knowledge of aviation medicine is essential. The literature on this subject appearing during the war was of such volume as to suggest that the topic could only be understood by specialists in aviation medicine. This book, presented in most readable form as a compact review of the medical problems associated with flying, is acceptable to all. It would be erroneous to presuppose that the book deals entirely with scientific aviation medicine as applied to war; a wealth of practical advice is readably available on such varied subjects as the advisability of pregnant women flying as passengers, night blindness, and also the effects of smoking on general health. The medical contra-indications to air travel presented in tabulated form will appeal to many as the most acceptable part of the volume. Free illustrations, diagrammatic and clearly reproduced photographs, and an excellent bibliography all add to the acceptability of this excellent volume.

*Notes on the Theory of Dental Surgery.* By NORMAN BLACK. Pp. 168. London: Staples Press Ltd. 1949. Price 12s. 6d.

This book is described as being a handbook on dental surgery and pathology for students preparing for their final examination. Modern methods of treatment are not mentioned and chemotherapeutic agents such as penicillin are completely ignored. The references to oral pathology are inadequate and would not give a student a true picture of the condition. An appendix devoted to local anaesthesia is included but this would have been improved by the incorporation of simple line drawings to clarify the text.

*Surgery for Nurses.* By JAMES KEMBLE, CH.M., F.R.C.S.ENG., F.R.C.S.ED. Pp. xiv+348, with 374 illustrations. Bristol: John Wright & Sons Ltd. 1949. Price 21s. net.

This admirable surgical textbook for nurses covers a wide field, clearly, concisely and dogmatically where necessary. The arrangement is good; chapters and sections are well headed, and the illustrations, some of which are in colour, are well chosen and profuse.

*Tom Cullen of Baltimore.* By JUDITH ROBINSON. Pp. 435, with 20 illustrations. London: Oxford University Press. 1949. Price 21s. net.

This is the life story of an outstanding medical man, who became head of the Department of Gynaecology at Johns Hopkins Hospital and taught in its medical school from its inception. Cullen was a great man who was well known and respected throughout his country and indeed the world. He had a remarkable career and from early days of anxiety and poverty he became a leader in the profession. The biography of a great man is always interesting but this tale is even more so because it includes the names of several other great medical men amongst whom are Dr Howard Kelly and Sir William Osler. Cullen had many interests besides gynaecology. He was a leading public figure and took a large part in public health and the famous library system of Baltimore. The interest of the reader is maintained throughout by the story which is always changing and always vital.

*Your Hospital.* By A. R. J. WISE, F.H.A. Pp. 239, with 50 illustrations. London: William Heinemann (Medical Books) Ltd. 1949. Price 15s. net.

The author, a hospital administrator of experience, writes for the enlightenment of the layman, but there is much that might be of interest even to the hospital worker. He tells of the early hospitals, of modern conditions and of how the future may be shaped. There is a short account of each speciality and service, showing how they fit in with the whole and how the public can take advantage of them. Other chapters describe the management of a hospital, the problems of catering and the design of modern institutions. A highly informative book which should give the public an insight into their new heritage.

*Introduction to Micro-organisms.* By LAVERNE RUTH THOMPSON, R.N., M.A., M.S. Pp. 454, with 73 illustrations. London: W. B. Saunders Company. Price 21s.

A small attractively bound volume. The quality of the paper and print is exceptionally high and the illustrations, including several good electron micrographs, are most refreshing.

The subject is presented in an interesting fashion for public health and welfare workers without previous knowledge of bacteriology; it might prove of value as a reference book for nurses.

The text covers prevalent infectious diseases both of temperate and tropical regions and the present edition incorporates most recent information likely to be of interest to those for whom it was written.

*Surgeon's Saga.* By ROBERTSON MCDOUALL. Pp. 330. London: William Heinemann (Medical Books) Ltd. 1949. Price 15s. net.

This book is written in the form of a novel, the surgeon being carried from his schooldays, through Glasgow University to London where he works during the blitz, and finally to Skye. There are many vivid pictures of medical life—general practice in the Gorbals, the overworked E.M.S. surgeon of war-time and the helpful psychiatrist. There is much sound sense and much thought-provoking material woven into the tale. This pleasantly written book is one we can heartily recommend, particularly to the young practitioner.

*Mayo Clinic: Diet Manual.* Pp. 529. London: W. B. Saunders Company. 1949. Price 20s.

This book, drawn up by the Committee on Dietetics of the Mayo Clinic, contains all the diets in ordinary use in that institution. With advancing knowledge of nutrition, increasing use is being made of special diets in the treatment of many disorders. The *Diet Manual* contains very little textual matter, just sufficient to explain the object of the diet, but it gives in fullest detail the foods and the quantities required. It is a first-class book of reference on the most approved present-day practice.

*A Surgeon's Domain.* By B. M. BERNHEIM, M.D. Pp. 217. Kingswood, Surrey: The World's Work Ltd. 1949. Price 9s. 6d. net.

The author, a surgeon at Johns Hopkins, describes medical training in America and especially his own progress till he joined the staff of a great hospital. Though written primarily for laymen it may well be read with profit by medical men, for he holds strong views on matters of the greatest interest to the profession.

*No Place to Hide.* By D. BRADLEY. Pp. 191. London: Hodder & Stoughton. 1949. Price 7s. 6d.

Writing in the form of a diary, the author, an American doctor, gives an account of the Bikini expedition which studied the effects of two atomic bombs exploded under experimental conditions. Dr Bradley concludes that there is no real defence against atomic weapons and there is no medical or sanitary safeguard for the peoples of an atomised area. The book is not all scientific data, but contains an interesting account of a pleasant trip amongst south-sea islands.

*Collected Papers of the Mayo Clinic and the Mayo Foundation.* Edited by R. M. HEWITT, B.A., M.A., M.D., and others. Volume XL, 1948. Pp. xii+918, with 116 illustrations. London: W. B. Saunders Company. 1949. Price 55s.

This annual publication from the Mecca of American medicine is a wonderful collection of modern ideas. It covers all fields of medical knowledge, and kindred papers are grouped together in sections so that they are readily accessible. The papers vary considerably, some are relatively short summaries of work which has appeared elsewhere, while others are relatively full. This excellent periodical is worthy of the attention of specialists in every branch of medicine.

*Introductory Botany.* By ALEX. NELSON, B.Sc., Ph.D., D.Sc. Pp. viii+479, with 121 figures. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 22s. 6d. net.

This book has been written as an elementary course in the science of plant life to serve as a basis of biological knowledge for the student going on to medicine or one of the kindred disciplines. It deals with classification, structure, morphology and methods of reproduction, also with physiology, genetics and the distribution of plants. The material is clearly presented and satisfactorily illustrated, and the book is to be strongly recommended to those who require an introduction to the subject.

*The Structure of Medicine and Its Place Among the Sciences.* By F. M. R. WALSHE, M.D., D.S.C., F.R.C.P., F.R.S. Pp. 26. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 1s. 6d.

This is the Harveian Oration for 1948, a very erudite and thought-provoking examination of the subject. "The need for rebuilding the foundations of medicine was never greater than to-day, when we are being swept along in a spate of new knowledge and new techniques, and have so little time for their due contemplation and integration."

*Medical Etymology.* By O. H. PERRY PEPPER, M.D. Pp. vi+263. London: W. B. Saunders Company. 1949. Price 27s. 6d.

In former days the student was prepared for his professional studies by a thorough grounding in the classical languages, and the new terms used in medical classes offered little difficulty. Now things are different, and to make good the deficiency Professor Perry Pepper has produced this excellent book. His material has been arranged in various sections which deal with the words employed in different fields of medical teaching. The book is not a dictionary defining the terms, but deals with origins and derivations though explanatory notes are often added. This useful reference work should be greatly appreciated by the harassed undergraduate.

*Living Anatomy.* By RONAN O'RAHILLY, M.B., M.S.C. Pp. x+88, with 7 figures. Oxford: B. H. Blackwell. 1949. Price 5s. net.

These notes are primarily intended to be read in connection with a practical class in topographical anatomy and should also serve as a brief summary of the subject. The requirements of clinical examination of the patient have been kept prominently in view. Chief stress has been laid on the surface orientation of deep soft tissue structures as many of the skeletal structures are so obvious. In addition, there is a series of appendices in approximate vertebral levels, dates of eruption of teeth, ossification centres and segmental innervation of muscles. A useful compilation.

*The Healing Touch.* By HARLEY WILLIAMS. Pp. 408, illustrated. London: Jonathan Cape. 1949. Price 15s. net.

Those who have enjoyed Harley Williams' earlier writings will welcome this new series of biographical sketches. William Knighton, James Clarke, William Jenner, Edwin Chadwick, T. S. Smith, Florence Nightingale and C. E. Brown Seguard are the principal characters, but shorter accounts of many others are also introduced. Perhaps the most fascinating story is that of the development of the Mayo Clinic—a piece of modern history that should be familiar to every medical man. Harley Williams has a pleasant touch and his present book will enthral the leisure hour.

*Obstetric Analgesia and Anæsthesia.* By F. F. SNYDER, M.D. Pp. viii+401, with 114 illustrations. London: W. B. Saunders Company. 1949. Price 32s. 6d.

This publication, based on forty-five years of practical experience and investigation in obstetrics, coincides with a flood of newspaper propaganda for the universal use of analgesia in childbirth. At a time when there persists some indifference to and inadequate knowledge of the problems of analgesia and narcosis in relation to parturition, an authoritative work such as this comes opportunely. The author stresses the great importance of the physiological, pharmacological and psychological factors involved. His observations on prenatal activity of the foetal respiratory mechanism and a detailed study of the influence of various drugs on the latter are of particular interest and value. The fact that the agent, trichlorethylene, and the relaxant, tubocurarine chloride, have not been included does not in any way lessen the enthusiasm with which the reviewer recommends this well-written and finely produced volume to all obstetricians and anæsthetists.

# Edinburgh Medical Journal





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*Penicillin and Other Antibiotics.* By G. W. S. ANDREWS and J. MILLER, with a foreword by Sir ALEXANDER FLEMING, F.R.S. Pp. 160, with 4 plates. London: Todd Reference Library. 1949. Price 7s. 6d. net.

The object of this book is to present a short scientific survey of the field of antibiotics and it may be fairly said to have been achieved. After a general discussion of antibiotic substances, the properties, production and the principles of the use of penicillin are dealt with in some detail. There are also good sections on streptomycin and tyrothricin.

*A Psychiatrist Looks at Tuberculosis.* By ERIC WITTKOWER, M.D. Pp. 152. London: The National Association for the Prevention of Tuberculosis. 1949. Price 12s. 6d.

Some knowledge of the human make-up is necessary for the practice of all forms of Medicine and certainly the tuberculous person during the course of his long and uncertain illness presents many psychological reactions which require patient and sympathetic handling. In this book Dr Wittkower describes the results of a long and painstaking study of the psychological aspects of tuberculosis, and his description of the various personality types and their reactions to the circumstances of the disease will be of the greatest help to all who have anything to do with these patients. Sufferers from tuberculosis come from all walks of life and belong to all personality types, and it is extremely doubtful if a statistician would be happy about some of the conclusions which Dr Wittkower draws. Whether we agree with the author's conclusions or not the value of his investigation is obvious, and the N.A.P.T., by fostering and publishing this research, has placed workers in tuberculosis further in their debt.

*The Pharmacologic Principles of Medical Practice.* By JOHN C. KRANTZ, Jr., and C. JELLEFF CARR. Pp. xv+980, with 94 illustrations. London: Baillière, Tindall & Cox. 1949. Price 55s.

This American textbook combines pharmacology and therapeutics in one volume. The subject matter is arranged according to the physiological systems of the body. A synopsis is given of the physiology and biochemical functioning of each system and then the drugs which may be used are described and their pharmacological actions discussed. Finally the clinical use of various preparations is assessed. A carefully selected and purposefully limited bibliography is given with each chapter with special emphasis on monographs and recent publications.

The excellent presentation of the subject in this well-known book makes pharmacology a live and interesting study instead of a dull collection of facts and doses to be memorised. The British names of some drugs are not given but this is a minor defect which does not seriously affect the value of the book as a whole. This volume can be most heartily recommended to both medical students and their teachers.

*Human Personality and Its Minor Disorders.* By WILLIAM HARROWES, M.D. Pp. vii+260. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 15s. net.

This book, as the author states, is founded on the psycho-biological concepts identified with the name and teaching of Adolf Meyer. It is a more or less formal interpretation of Meyer's work and consists essentially of an analysis of his personality studies as shown by the *Life Chart* and the *Scheme of Organisation of Action Potential*. The assets of the normal personality are discussed in detail and the whole is brought into relation with the organisation of the person's life, especially the emotional and social factors. The chapter on treatment is disappointing and not informative. As a whole, however, the book can be recommended as a good account of Meyer's work and methods.

*Blood Transfusion.* Edited by GEOFFREY KEYNES. Pp. 586, with 110 illustrations. Bristol: John Wright & Sons Ltd. 1949. Price 52s. 6d.

*Blood Transfusion.* By ELMER L. DEGOWIN, ROBERT C. HARDIN, and JOHN B. ELSEVER. Pp. 587, with 200 illustrations. Philadelphia and London: W. B. Saunders Company. 1949. Price 45s.

These two books, published almost simultaneously, and both founded on the experiences of the war years, inevitably invite comparison.

The English book is the work of seven contributors in addition to the editor who himself contributes an interesting historical chapter (40 pages; the subject is dismissed in 4 pages by the American authors). Dr Ronald Bodley Scott provides an excellent account of the indications and complications of blood transfusion and the technique is described by Dr A. Till, whilst Professor R. W. B. Ellis considers the special problems of transfusion of infants; Dr H. F. Brewer follows with a detailed description of the blood groups, the techniques employed in their detection and in the preparation of test sera, their inheritance, and their clinical significance; he also describes the organisation of the donor service (chiefly for "direct" transfusion) and of a hospital transfusion department and, with Mr F. W. Mills, gives an account of the particular service with which they are associated and of the psychology of blood donors (this chapter ignores too much the organisation and problems of the regional service organised by the Ministry of Health). Sir Lionel Whitby writes on storage and preservation (his account, based largely on his war-time work, might well have been made more general), Dr R. I. N. Greaves on the preparation of plasma, plasma fractions and substitutes. Considered individually the chapters—or, rather, essays—are good, yet the book as a whole leaves the reviewer unsatisfied; perhaps because of the piecemeal treatment, perhaps because the subject is changing so rapidly that no account can be wholly adequate; perhaps because so many of the present day problems are ignored or touched upon so lightly.

The American book, more uniform in character, covers similar ground but with different emphasis. The authors are concerned more with the practical details of transfusion technique in laboratory, hospital, and organising office, and the descriptions given are suited to workers of all grades. The clinical sections and that on the theoretical aspects of blood groups are brief—perhaps too brief, were it not that the book seems to be intended for those who supply a transfusion service rather than for those who use it. The descriptions of plasma preparation, etc., and of organisation are based exclusively on American practice (as those of Keynes' book are on British).

The two books, because of their different origin, development and scope are complementary and both are needed by the transfusion officer.

*Practical Aspects of Thyroid Disease.* By GEORGE CRILE, Jr., M.D., F.A.C.S. Pp. xviii+355, with 101 figures. London: W. B. Saunders Company. 1949. Price 30s. net.

In this admirably compact and readable little book Dr Crile presents current American views on the diagnosis and treatment of thyroid disease. Written as it is by a surgeon, the account has a natural bias in favour of the surgical approach, and some of his conclusions would be disputed by physicians in this country. The figure of 15 per cent., which he gives as the proportion of cases of hyperthyroidism showing a satisfactory response to thiouracil, seems unaccountably low, and the statement that all cases of discrete adenomata (even if symptomless) should be subjected to operation might not perhaps be accepted without question. Obviously considerably more importance is attached to determinations of the basal metabolic rate than is done in this country. Both diagnosis and assessment of progress may depend largely on it rather than on the clinical judgment of the physician. On the whole, however, the book is well balanced and practical. It is plentifully illustrated with diagrams and photographs, all of a high standard of excellence.

## NEW EDITIONS

We regret that the following book reviewed on page 508 was incorrectly designated:

*Recent Advances in Cardiology.* By T. EAST, M.A., D.M., F.R.C.P., and C. BAIN, M.C., D.M., F.R.C.P. Fourth Edition. Pp. x+454, with 98 figures. London: J. & A. Churchill. 1948. Price 24s.

*Clinical Methods.* By Sir ROBERT HUTCHISON, Bart., M.D., LL.D., F.R.C.P., and DONALD HUNTER, M.D., F.R.C.P., with the assistance of R. R. BOMFORD, D.M., F.R.C.P. Twelfth Edition. Pp. xv+484, with 103 figures and 27 plates. London: Cassell & Co. Ltd. 1949. Price 17s. 6d. net.

The original "Hutchison and Rainy" was published in 1897 and since then the successive editions have held a position of unrivalled popularity. Much revision has been necessary to bring the edition of 1940 up to date. While the general arrangement and approach to the subject remains the same, a great amount of new material has been included. The high standards of earlier editions have been maintained and this little book will continue to hold its place in the affections of undergraduates and practising doctors.

*Diseases of the Liver, Gall Bladder and Bile Ducts.* By S. S. LICHTMAN, M.D., F.C.A.P. Second Edition. Pp. 1135, with 147 illustrations and 2 colour plates. London: Henry Kimpton. 1949. Price 90s. net.

This fine reference book on the liver has been brought completely up to date since its publication seven years ago. Recent advances in knowledge of liver-damaging agents are fully described and a new chapter has been added on virus hepatitis with a discussion on its relationship to cirrhosis. Aspiration biopsy has proved a relatively safe technique for studying tissue changes in liver disease and its place in diagnosis and in the assessment of liver-function tests and therapeutic measures is well considered. The whole volume, which is splendidly produced, deals systematically with every aspect of liver, gall bladder and bile duct, anatomy, physiology and pathology, as well as giving full clinical features and treatment. There is an excellent bibliography. That such a large and comprehensive work should be devoted to one organ alone is a measure of the growing complexity of medical science, but this book is outstanding in its field.

*A Descriptive Atlas of Radiographs.* By A. P. BERTWISTLE. Seventh Edition. Pp. 622, with 980 illustrations. London: Henry Kimpton. 1949. Price 50s. net.

The author states in his introduction that this book is written by a clinician for clinicians. As such it should prove of value to physicians and surgeons requiring a working knowledge of X-ray interpretation and to those reading for higher examinations. Emphasis is placed on the reproduction of X-rays rather than on matters of technique and description. The reproductions are of good quality. Few common conditions escape illustration and many rare ones are also included. Brief clinical notes accompany each illustration.

*Fractures and Dislocations in General Practice.* By J. P. HOSFORD, M.S., F.R.C.S. Second Edition. Revised by W. D. COLTART, F.R.C.S. Pp. x+288, with 87 illustrations. London: H. K. Lewis & Co. Ltd. 1949. Price 21s. net.

This small book contains in concise but readable form a surprisingly large amount of information about all the common fractures and dislocations. The reviser admits that the general practitioner plays little part nowadays in the technical treatment, though he is still concerned with the immediate first-aid care of the injured, and with the important after-care during the interval between discharge from hospital and return to work. The book will appeal most to the final year medical student.

*Geriatric Medicine: The Care of the Ageing and Aged.* Edited by EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P. Second Edition. Pp. 773. London: W. B. Saunders Company. 1949. Price 60s.

In this book many authorities with outstanding knowledge and experience in their various fields cope with the problems of chronic progressive disease especially affecting the aged. Considerable new material has been added, particularly in connection with the care and guidance of the so-called "normal" ageing patient. Special care has also been given to cardiovascular disorders.

This book is now a classic, unique in its field, as it presents the problems to the general practitioner and to all specialists of general medicine, and does not pretend to be a textbook for a "speciality" in the usually accepted sense, the statistical material being reduced to the minimum.

*Minor Surgery.* Edited by Sir HENEAGE OGILVIE, K.B.E., D.M., M.CH., F.R.C.S., and WILLIAM A. R. THOMSON, M.D. Second (Revised) Edition. Pp. xiv+192, with 34 illustrations. London: Eyre & Spottiswoode Ltd. 1949. Price 14s. net.

This book is made up mainly of a series of already published articles reputedly revised to make them suitable for inclusion in the book. In most of the chapters, the details given are too few to be a real use to the beginner in minor surgery and too many for those of moderate experience. In short, it is difficult to see why the editors bothered, and why many of the contributors who are well known in surgical circles allowed their names for a second time to be connected with such an ineffectual production.

*A Short Practice of Surgery.* By HAMILTON BAILEY, F.R.C.S., and R. J. MCNEILL LOVE, F.R.C.S. Eighth Edition. Part V. Pp. iv+242, with 202 illustrations. London: H. K. Lewis & Co. Ltd. 1949. Price £2, 12s. 6d. the set.

With the publishing of Part V the eighth edition of this well-known book is complete. Although the text and general lay out have not altered appreciably, yet there are included several new illustrations in this edition. This book is designed to teach the student by picture rather than by words. The illustrations are descriptive, very numerous and of a high quality. Since the pictures are easily retained in the memory, it will always remain a popular book with undergraduates.

*Campbell's Operative Orthopaedics.* Edited by J. S. SPEED and HUGH SMITH. Second Edition. Pp. xxiii+1643 (2 volumes), with 1141 illustrations (4 in colour). London: Henry Kimpton. 1949. Price £7, 10s. net.

This second edition of this very fine work by Campbell and his associates is altered in its purpose from the first in that it is written primarily for the fellowship man or resident, keeping in mind the limits of his experience. For this reader much preliminary data and a great deal of new material has been added. It would appear that for any orthopaedic condition requiring surgery every possible operation is given in full detail and with, in most cases, excellent line drawings. Careful attention is given to the details of technique and to the post-operative care. The rare or less common lesions are dealt with more fully than those more usually encountered, on the assumption that the readers will be well versed in the more common conditions. Three new chapters—pre-operative and post-operative care, peripheral nerve injuries, and amputations—have been added, while new sections on mould arthroplasty, ruptured intervertebral discs, and difficult and unusual non-union, have been written.

One feels that a little more advice should have been given to the younger readers on the choice of procedure, as each lesion seems to have so many ways of being treated.

This is certainly a magnificent compilation and will be of immense value for every one in this special branch of surgery.

*A Textbook of Pathology, General and Special.* By J. M. BEATTIE, M.A., M.D., D.Sc., and W. S. CARNEGIE DICKSON, M.D., B.Sc., F.R.C.P.E. With collaboration of A. MURRAY DRENNAN, M.D., F.R.C.P.E. Fifth Edition. Pp. 1582, with 802 illustrations and 21 coloured plates. London: William Heinemann (Medical Books) Ltd. 1949. Price £8, 8s. net.

Since its first appearance forty years ago "Beattie and Dickson" has steadily increased in popularity and may be regarded as the leading British textbook on the subject. The authors have aimed at combining the special advantages of a standard textbook with those of a book of reference. The general plan and the arrangement of the material remains as in former editions, but the extraordinary advances in knowledge during recent years have necessitated many changes in the matter both by deletion and by addition. A special feature of this edition is the section on diseases of the nervous system which has been particularly well done.

The technical production of the work is excellent; the vast number of illustrations have been well chosen and are of the greatest value in a work of this kind.

In the present edition, though the pagination remains continuous, the book has been divided into two volumes to facilitate easy handling.

The authors are to be congratulated on making a further contribution of first-class importance to British pathology.

*Cunningham's Manual of Practical Anatomy.* Vol. II, Thorax and Abdomen. Eleventh Edition. Revised by J. C. BRASH, M.C., M.A., M.D., F.R.C.S.E. Pp. x+488, illustrated. London: Oxford Medical Publications. 1949. Price 21s. net.

The present edition, though shorter than previous ones, continues their main objectives—to provide a detailed account of the body which can be used as a guide to dissection. The production of the work is of the high order to be expected.

*Textbook of Medical Treatment.* By various authors. Edited by D. M. DUNLOP, L. S. P. DAVIDSON and J. W. MCNEE. Fifth Edition. Pp. xvi+909, with 40 figures. Edinburgh: E. & S. Livingstone Ltd. 1949. Price 35s.

In the ten years since the appearance of this textbook it has attained a unique place in British medicine, and the present edition well maintains the high standard of the earlier editions. Therapeutic advances in the past decade have been phenomenal and the pace continues. It has been necessary, therefore, to make quite considerable changes in this book, both by way of addition and deletion. The chapters on nervous diseases, fevers, venereal diseases and penicillin have been revised by new contributors and new sections have been included on the care of the aged, on dehydration and hypochloræmia and on the anti-histamines.

The production of the book is a credit to its publishers and printers and the very reasonable cost of this invaluable work should guarantee a widespread popularity.

*Food Inspection Notes.* By H. HILL, F.R.SAN.I., F.S.I.A., A.M.I.S.E., and F. DODSWORTH, M.R.SAN.I., M.S.I.A. Third Edition. Pp. viii+125. London: H. K. Lewis & Co. Ltd. 1949. Price 7s. 6d. net.

The authors, two experts, have sought to sift essential information from many sources in order to provide public health students with a handy summary of the subject.

*Sanitary Science Notes.* By H. HILL, F.R.SAN.I., F.S.I.A., A.M.I.S.E., and E. DODSWORTH, M.R.SAN.I., M.S.I.A. Second Edition. Pp. v+135. London: H. K. Lewis & Co. Ltd. 1949. Price 7s. 6d. net.

This is in no sense a textbook, but a condensation of information required by students of sanitary science. It has been fully revised and brought up to date.



*Acute Injuries of the Head.* By G. F. ROWBOTHAM. Third Edition. Pp. xx+480, with 259 illustrations (34 in full colour). Edinburgh: E. & S. Livingstone Ltd. 1949. Price 35s. net.

Rowbotham's well-known monograph now needs no introduction or recommendation to the medical profession. In this new edition 58 new illustrations, 22 of which are excellent coloured photographs, have been added, and the resulting rearrangement has brought many of the illustrations into closer relation with the relevant text.

The alterations in the text are not extensive. They include amendments to the paragraphs on chemotherapy and antibiotics to bring them up to date; the separate description of "diffuse" and "localised" acute subdural hæmorrhages; a new section on status epilepticus; enlargement of the sections on alloplastic materials for the repair of skull defects and on plastic operations for closure of defects in the scalp; advice on the treatment of electrical burns of the scalp; a "summary of the lessons learned during the war"; and a new final chapter on "The Residual Illness." All these are improvements and the new chapter is a particularly valuable addition, being an authoritative and helpful review of the post-concussional syndrome.

## BOOKS RECEIVED

- ALLEN, CLIFFORD, M.D., M.R.C.P., D.P.M. *The Sexual Perversions and Abnormalities.* Second Edition. (*Oxford University Press, London*) 25s. net.
- BENNETT, REGINALD R., B.SC.(LOND.), F.I.C. Revised by ROLFE, H. G., B.SC., A.I.C., PH.C. *Materia Medica and Pharmacy: for Medical Students.* Fifth Edition. (*H. K. Lewis & Co. Ltd., London*) 16s. net.
- CHATTON, MILTON, A.B., M.D., MARGEN, SHELDON, A.B., M.D., and BRAINERD, HENRY D., A.B., D.M. *Handbook of Medical Management.* (*University Medical Publishers, Palo Alto, California*) \$3.00
- FLOREY, H. W., M.A., M.D., PH.D., F.R.S., CHAIN, E., M.A., PH.D., F.R.S., HEATLEY, N. G., M.A., PH.D., JENNINGS, M. A., M.A., B.M., SAUNDERS, A. G., M.A., M.B., D.PHIL., ABRAHAM, E. P., M.A., D.PHIL., and FLOREY, M. E., M.B., B.S. *Antibiotics. Volumes I and II.* (*Oxford University Press, London*) £8, 8s. net, per set.
- GROB, M., and ROSSI, E. *Einführung in Die Moderne Diagnostik der Angeborenen Angiokardiopathien.* (*Benno Schwabe & Co., Verlag, Basel*) Fr. 14
- HEARDMAN, HELEN. *Relaxation and Exercise for Natural Childbirth.* (*E. & S. Livingstone Ltd., Edinburgh*) 9d. net.
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